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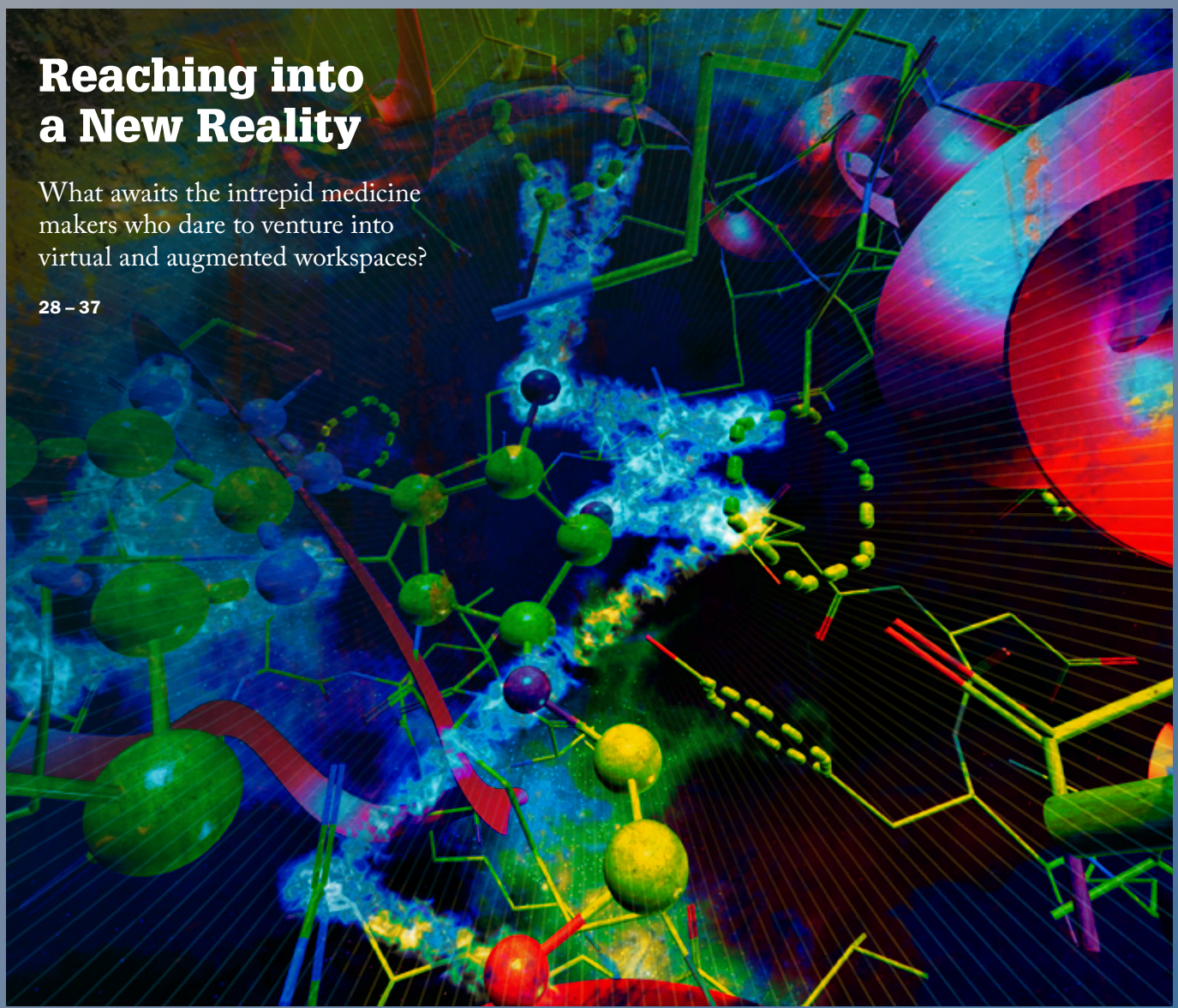

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Online this Month

Sitting Down With….. Steve Turley

Steve Turley discusses his early career and his role as Managing Director of UCB for the British and Irish Isles on page 51 in Sitting Down With, but the conversation continues on our website with an extended version of this interview.

http://tmm.txp.to/1016/turley

The Power List 2017

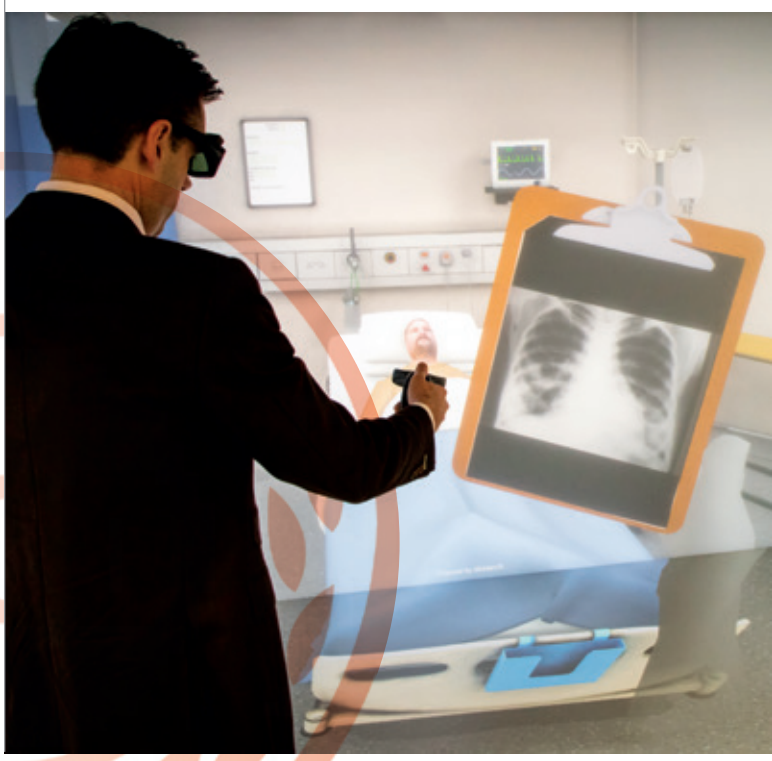
2016 is beginning to draw to a close, which means The Medicine Maker 2017 Power List will be here before you know it! Nominations for the 2017 list will close on February 1, 2017. Did you agree with the 2016 list (available at: https://themedicinemaker.com/power-list/2016/)? Which other esteemed members of the drug development and manufacturing community would you like to see featured on the list? And which unsung heroes do you believe deserve more recognition for their work? You have the power to decide.

Nominate now: http://tmm.txp.to/2017/powerlist
Or email: james.strachan@texerepublishing.com

The Buzz of a Virtual Reality Experience

As our experts describe in this month's cover feature on page 28, a virtual reality experience is famously indescribable. Editor, Stephanie Sutton, described her experience with augmented reality at the 2016 Interphex trade show in a previous editorial, which can be read online (http://bit.ly/2eVDc0K). More recently, Associate Editor, James Strachan, took a trip to the UK's Keele University to learn how virtual reality is being used by students studying pharmacology. You can read James' full experience with virtual reality online.

http://tmm.txp.to/1016/Keele



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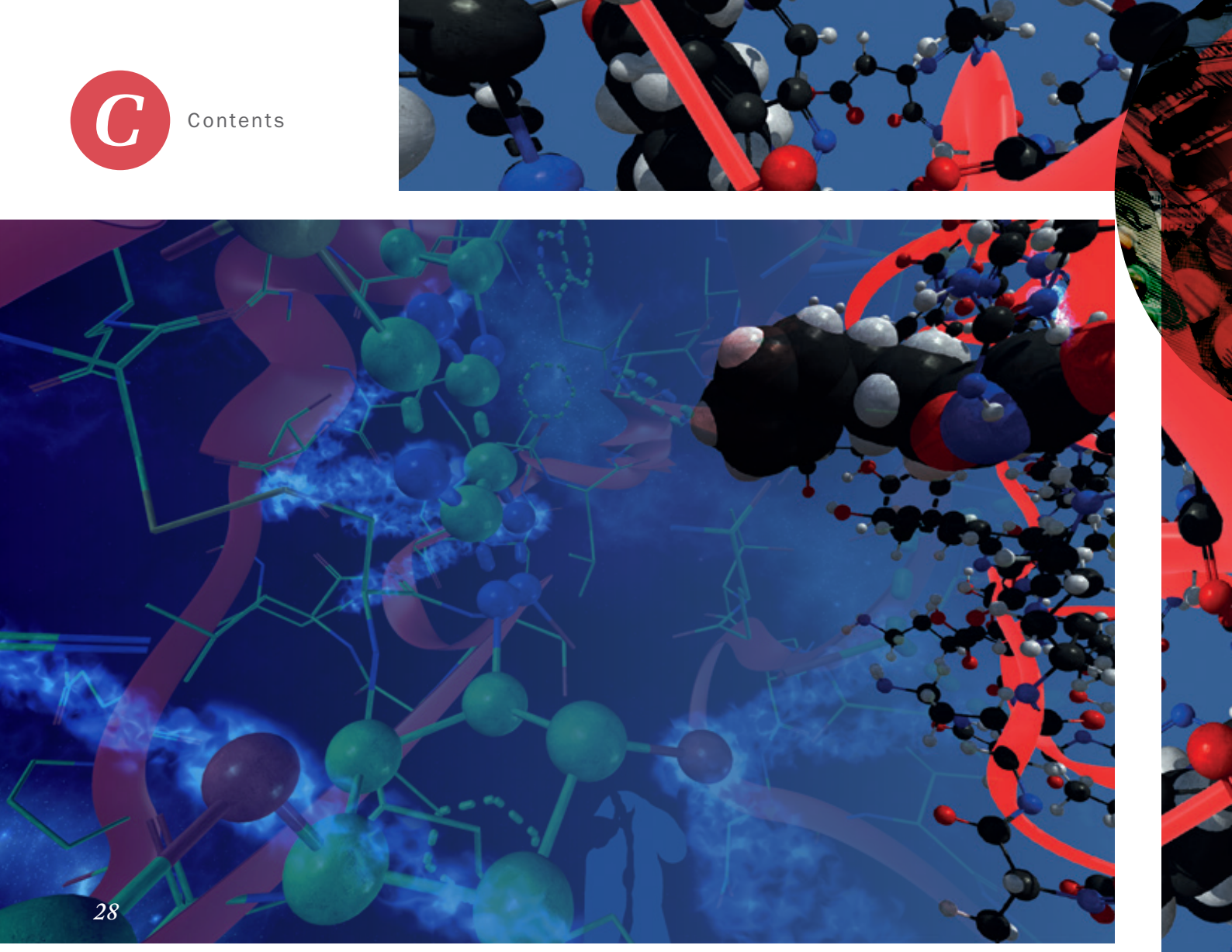

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the **Medicine Maker**

ISSUE 24 - NOVEMBER 2016

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Distribution:
The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing Ltd and is distributed in the USA by UKP Worldwide, 1637 Stelton Road B2, Piscataway, NJ 08854.
Periodicals Postage Paid at Piscataway, NJ and additional mailing offices
POSTMASTER: Send US address changes to The Medicine Maker, Texere Publishing Ltd, C/o 1637 Stelton Road B2, Piscataway NJ 08854
Single copy sales £15 (plus postage, cost available on request tracey.nicholls@texerepublishing.com)
Annual subscription for non-qualified recipients £110

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The Times They Are a-Changin'

What impact will Brexit, a new US President, and a flood of new technologies have on the industry?

Bob Dylan was seen as an unorthodox choice for the recipient of the 2016 Nobel Prize in literature – and he was also referenced by Robert Chew from Commissioning Agents Inc, at the ISPE's recent Facilities of the Future event. Chew explained that the times are indeed changing, both inside and outside the pharma industry. But not all changes can be anticipated – the outcome of the UK's referendum on its EU membership and the result of the US elections both defied the predictions of statisticians.

Change was a key theme at the ISPE event and although discussions during the networking breaks often veered towards Brexit, the US elections, and the uncertain impact on science, the overall focus of the conference was on the positive changes shaping the industry, such as the development of exciting new technologies. Margaret Prendergast, a bioengineer at BioBots, discussed the possibilities of 3D printing in automating biology. We've delved into the potential of 3D printing in pharma manufacturing before in The Medicine Maker (1), but Prendergast focused on the area of organ printing, which could potentially revolutionize research and development, as well as the lives of patients waiting for transplants. Meanwhile, Tyler McQuade from the US Defense Advanced Research Projects Agency (DARPA) discussed progress in making both small- and large-molecule drugs on demand. He envisions a transportable box that can be taken to remote locations, including battlefields, where the push of a button manufactures the required medicine – we also covered this hot topic earlier this year (2).

Such technologies almost sound too futuristic to be true, but both Prendergast and McQuade assured attendees that progress is being made rapidly, with McQuade adding that a number of big pharma companies have already contacted DARPA to get involved with the work. Another technology briefly mentioned during the event was the advent of augmented reality and virtual reality in manufacturing – we discuss this in great detail in this month's cover feature on page 28.

These technologies are on the horizon and are worth watching closely, but other changes lie just around the corner. A key takeaway from the ISPE event was that if it can be automated, it will be automated. In fact, jokes were made that automation in the future will only require one man and a dog. The dog's role will be to keep the man away from the automation, and the role of the man will be to feed the dog…

Jokes aside, big changes are coming. No change is ever straightforward, but unlike politics, at least technological changes can be better planned for.

Stephanie Sutton
Editor

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Upfront

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

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

Brainiacs in the Bar

A new podcast series gives listeners the chance to eavesdrop on a conversation between scientists in a bar

What?

The pharma industry doesn't have always have the best image in the eyes of the public, despite conducting lifesaving research. It has often been said that pharma can do a better job of telling its story – and what better place to do that than in a bar? "Two Scientists Walk Into a Bar" is a new podcast series developed by Genentech where scientists from the company team discuss what they do in the lab and why it matters. According to Robin Snyder, director of science communications at Genentech and the creator of the podcast, the aim is to give "listeners the sense that they're eavesdropping on some brainiacs 'talking shop' over cocktails in a bar". There will be eight episodes in the first season, with topics ranging from cancer to pain to superbugs.

"We see this podcast as a way to bring science to life and to convey what science means to us. The topics are serious, but the tone of the discussion is breezy, even a little irreverent at times, which is why it's set in a bar," says Snyder. "We hope that the scientific community in both industry and academia find it informative and entertaining, but we also hope that it helps bring the excitement of scientific inquiry and drug discovery to non-scientists."

Why?

Snyder says that Genentech is always looking for new ways to showcase the company's science. "I'm a huge podcast fan so I thought it might be an interesting avenue to explore," she explains. "Like everything we do at Genentech, the decision to go with the podcast was

actually based on data in the end. We did a survey of our postdocs to ask about media consumption habits and were surprised to learn that podcasts were their second most popular source for information behind scientific journals."

Who?

The show is hosted by Jane Grogan (pictured), principal scientist of cancer immunology at Genentech, who previously moonlighted as a radio host during her days as a grad student in Australia. "Jane loved the idea right away, and if you listen to one of our podcasts you can tell how at ease she is and how much she enjoys being 'on the air' again," says Snyder. "Though she did take some convincing because I had to promise her that doing the show wouldn't involve much time being away from her lab."

The first episode featured Ira Mellman, Genentech's Vice President of Cancer Immunology, who discussed breakthroughs in cancer immunology. The second episode featured Morgan Sheng, Vice President of Neuroscience and Molecular Biology, who told the story of how a family of Pakistani street performers helped scientists identify a novel target for treatment.

Where?

The podcasts are available online at: http://bit.ly/2eMPGJ0. Episodes are released bi-weekly.

"I think there is a real appetite for this type of accessible science," says Snyder. "We've had a lot of positive feedback from journalists, the scientific community, schools, and, of course, our own employees." *JS*

Side Effects? What Side Effects?

Patients don't always read drug risk information – even when they say they do

A study that used eye-tracking technology to find out whether or not consumers read the risk information on branded drug websites found considerable disparity between reported reading and actual reading.

"In general, eye-tracking data told us that participants had limited to no risk reading, but approximately 80 percent self-reported that they had read half or more of the risks," says Mariea Hoy, a professor in the School of Advertising and Public Relations at the University of Tennessee, and lead author of the study (1).

Of the 12 risks mentioned on the website, nearly half of the participants recalled no risks at all, 17.2 percent recalled just one, and none recalled more than four. "In the case of seasonal allergy drugs, our interviews suggested that perceived familiarity was the primary reason patients didn't read the risk disclosures," says Hoy (pictured). "The participants thought they knew all about antihistamines and said they weren't concerned about looking for risk information – which prompted optimism bias – resulting in them totally missing the novel risks for the particular drug."

So how can we make sure patients are reading and understanding risk and side effects information? According to Hoy, one simple mechanism could be to present the risks before the benefits. "Eye tracking shows that people start at the top of the screen and then look down, searching for the benefit information. By putting the risk information before the benefits, it may make the information more noticeable."

The one problem with this solution, however, is that few marketers would be willing to present negative information before product benefits. Hoy suggests a compromise where drug manufacturers present any risks that are novel or unique to the drug class first. "Another method that could be employed would be to create a sense of 'unfamiliarity' if there are risks that are unique or novel to the drug class," says Hoy.

There are still a number of questions that Hoy would like to see answered. She

adds, "An important next step would be to see how these findings might differ based on the individual's familiarity with the drug category, or the severity of the condition the drug treats, or whether the person is gleaning information on behalf of themselves or another." *JS*

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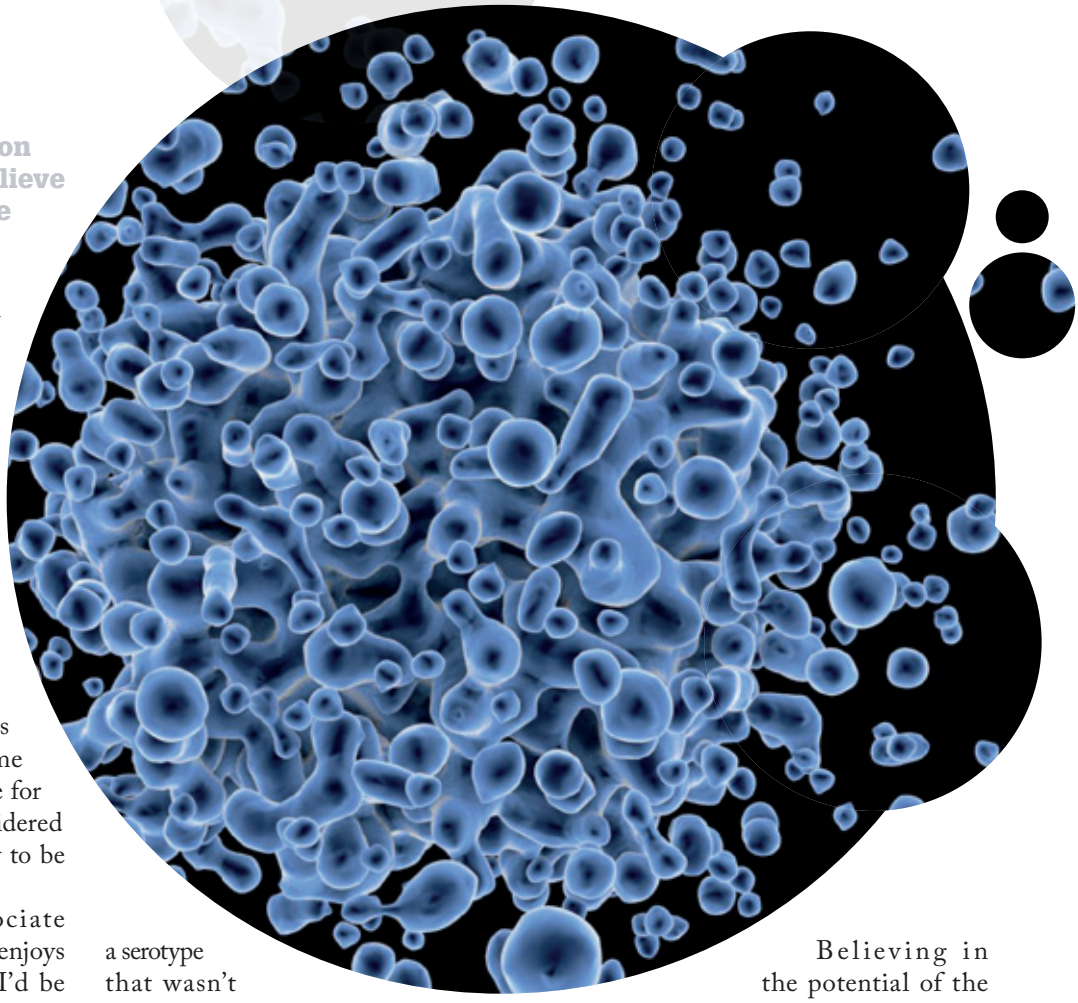
The Cold War

Is a vaccine for the common cold impossible? Many believe so, but some scientists are up for the challenge



The common cold is more than just a nuisance: it is one of the leading causes of community-acquired pneumonia requiring hospitalization in children, and can cause serious problems for people with asthma and chronic obstructive pulmonary disease. The majority of common colds are caused by rhinovirus, but so far scientists haven't been able to develop a vaccine. Why? Rhinovirus has 170 serotypes (or strains), whereas poliovirus (which is in the same family) only has three. A vaccine for the common cold has been considered by many in the pharma industry to be an insurmountable problem.

But Martin Moore, Associate Professor at Emory University, enjoys a challenge. "I didn't know if I'd be able to tackle it, but that's what makes it fun!" says Moore. "We delved into old literature from the 1970s – and found that teams from the University of Virginia, the US National Institutes of Health, and the UK Medical Research Council's Common Cold Research Unit had shown that a monovalent-killed rhinovirus vaccine could induce protective antibodies and prevent colds when volunteers were challenged with the homologous strain."

The vaccines were safe and worked fairly well in the clinic, but the number of serotypes was a problem – the original researchers managed to pick out 10 different serotypes and combine them into one shot, but it wasn't enough. When they challenged someone with a serotype that wasn't in the vaccine, they'd catch the cold.

In Moore's study, the team managed to combine 50 different serotypes into one vaccine (1). "Others have looked for conserved proteins and protein regions among the rhinovirus serotypes. But we want to utilize natural immunogens, and we wanted to base our vaccine on a clinically successful approach – killed virus. So we just mixed them together – a solution that in retrospect seems simple but was not obvious. Thanks to modern technology, we were able to include a higher quantity of each strain in our vaccine compared to the old studies, and that made the difference," says Moore. The vaccine proved to be broadly and potently immunogenic in rhesus monkeys.

Believing in the potential of the vaccine, Moore has co-founded a startup company to take the project further: Meissa Vaccines. The key question his team now faces is how to manufacture and scale up the vaccine. "The process would be similar to inactivated poliovirus vaccine," says Moore. "We are looking into specific patient populations, the molecular epidemiology of the virus, and manufacturing processes – which is our major challenge." The company also has support from the US National Institute of Health to develop a manufacturing plan. *JS*

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Efficacy vs Effectiveness

Tightly controlled trials are poor predictors of real-world outcomes

Traditional efficacy trials are not enough to guarantee that a drug will work in the more diverse population seen in the clinic, according to researchers who evaluated the effectiveness of an inhaled drug combination for chronic obstructive pulmonary disease (COPD) in everyday clinical practice (1).

"Efficacy studies are limited in their usefulness to clinicians as they are often restricted in their inclusion criteria, meaning that they show what the drugs can do in a controlled setting but not necessarily what they can do in the real world," says Jørgen Vestbo, first author and professor of respiratory medicine at the University of Manchester, UK.

In fact, the authors suggest that fewer than 10 percent of COPD patients would normally be eligible for efficacy trials, since they typically exclude anyone with a coexisting condition. The investigators carried out a randomized study in patients under the care of general practitioners, without the frequency, monitoring or strict eligibility criteria of a controlled trial, to allow for the variation in adherence, dosing frequency, and inhaler technique seen in unsupervised patients.

Rather than efficacy under ideal conditions, the trial assessed the real-world effectiveness of an inhaled combination of fluticasone furoate and vilanterol. The results showed that a broad population of COPD patients benefitted from the inhalant combination, without a significantly greater risk of adverse effects. The authors argue in their paper that incorporating effectiveness trials as a standard component of the translational process would provide much clearer evidence on which to base clinical decisions.

"It's not a question of either/or," says Vestbo, "Efficacy studies are still needed; however, effectiveness studies are also required to ensure that the drugs have the expected effects in the real world." *WA*

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The Great Off-Label Debate

The FDA consults stakeholders over plans to loosen restrictions on off-label drug marketing in the US

As part of a review on the regulatory framework around the promotion of off-label marketing, the FDA recently held a two-day public hearing to give patients, caregivers, advocacy groups, physicians and pharma companies the opportunity to discuss the pros and cons of disseminating off-label drug information (1). The aim of the meeting was to find out how increased communication from pharma companies on off-label use might impact public health.

Pharma companies have lobbied Congress for some time to loosen FDA restrictions against off-label drug marketing. Since doctors are allowed to prescribe medicines for unapproved uses, pharma companies have argued that they should be able to disseminate truthful information about off-label drug use and to discuss relevant research outside the scope of the initial FDA review of a drug, or research that occurred after a drug was approved.

On the first day of the meeting, held on November 9 at the FDA's White Oak Conference Center in Silver Spring, many of the discussions revolved around whether the First Amendment gives companies the right to talk about off-label product use – a growing problem for the FDA given that some companies have initiated free speech lawsuits against the agency. In a statement about the hearing, Pharmaceutical Research and Manufacturers of America (PhRMA) President and CEO Stephen J. Ubl, explained (2), "The market for medicines is changing rapidly as alternative payment models proliferate and novel decision tools like value frameworks are being applied[...] it is important that biopharmaceutical companies be able to share appropriate science-based information."

A great deal of emphasis was placed on off-label drug use in children because so few pediatric medicines are available, which makes off-label drug use inevitable. On the second day of the hearing, however, some patients gave their account of how they had been injured after receiving off-label medicines or using an off-label medical device.

According to a recent poll by Consumer Reports, 84 percent of Americans do not want companies to be allowed to advertise drugs for a use that has not been approved by the FDA (3). Lisa McGiffert, Director of Consumer Reports, spoke at the hearing and added, in a press release, "Relaxing the current rules would dismantle a legal firewall that has protected Americans from false and misleading drug advertising for more than half a century." She referred to the Congressional decision to outlaw off-label marketing in 1962, following the widespread off-label promotion of the drug thalidomide, which led to birth defects worldwide.

No decision will be made following the meeting, but the FDA hopes to learn more about the possible benefits of off-label drug marketing for clinical decision making, research, coverage, and reimbursement. *JS*

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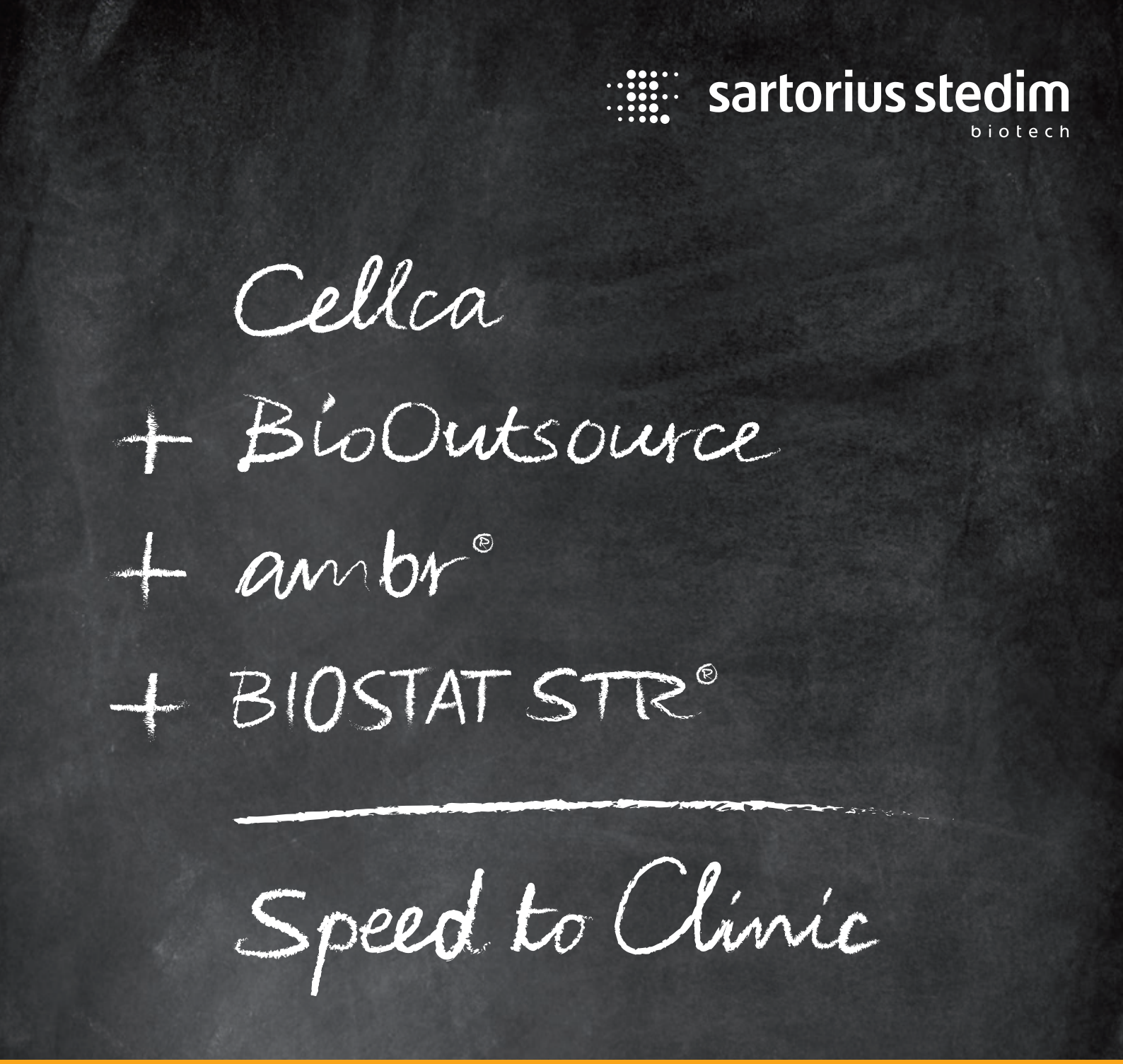

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Generics Deliver Savings

Generic drugs are cheaper than branded medicines, but how much do they save payers each year?

The latest Generic Drug Savings and Access Report, commissioned by the Generic Pharmaceutical Association, found that generic medicines save the US around $230 billion each year (1). The findings build upon those of a report published last year, which found that generics save the European Union around €100 billion ($112 billion) per year (2). Check out our infographic for more of the findings.

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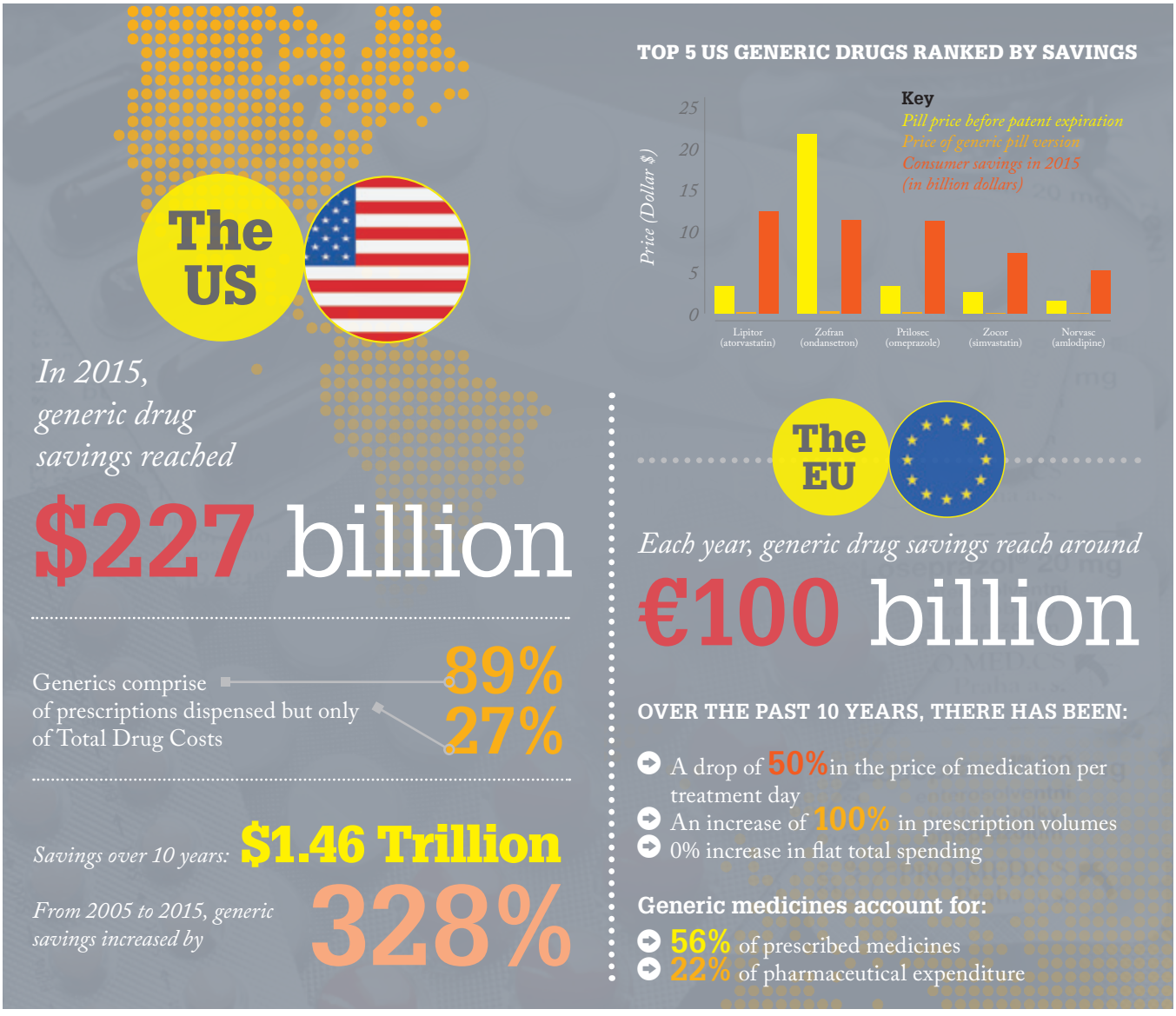

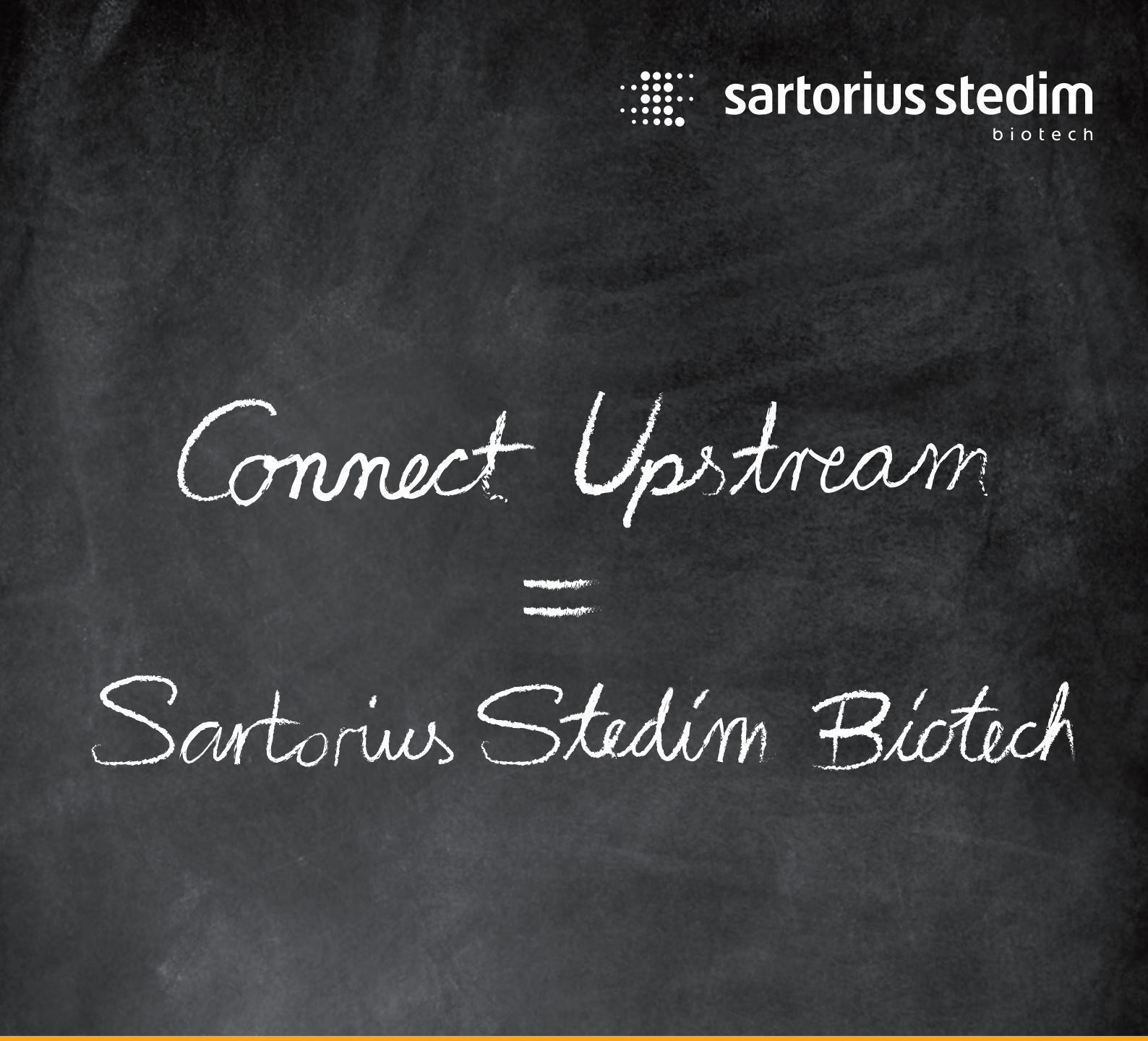

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Business-in-Brief

Collusion, pollution, and a pricing victory for pharma in California… What's new in business?

This month sees some interesting developments in the US Department of Justice's (DOJ's) investigation into price fixing and collusion among generic pharma companies, as well as a recent report into antibiotic pollution in the pharma industry.

Investigations

- Generic pharma companies could face charges of price collusion following a two-year DOJ investigation. $8.5 billion in market value was wiped off generic company shares on Thursday, November 3, after it was revealed the DOJ are preparing criminal charges after their longstanding investigation into suspected price collusion. Bloomberg broke the story, quoting "people familiar to the matter," who said that the investigation "now spans more than a dozen companies and about two dozen drugs."
- US lawmakers, Bernie Sanders and Elijah Cummings, have called for the DOJ to investigate possible collusion between Eli Lilly, Novo Nordisk and Sanofi over insulin prices. In a letter to the regulators, they point out that the drugmakers have often increased the price of insulin in unison.

Elections

- Californians voted against the "California Drug Price Relief Act," by a margin of 8 points – 54 percent for, and 46 percent against. The proposition would have prohibited state health programs from purchasing prescription drugs that cost more than the lowest price paid by the Department of Veterans Affairs. Pharma spent over $100 million supporting the successful "no" campaign.
- Pharma stocks were among the few risers following the result of the US Presidential election. Shares in AstraZeneca and GlaxoSmithKline rallied by more than 2 percent, while Shire was up more than 8 percent.

Manufacturing

- A new report by Changing Markets has found evidence supporting the claim that pollution from pharma plants is contributing to antibiotic resistance. Researchers sampled water from three factories in India and found evidence of drug-resistant bacteria.
- Merck KGaA has opened a new $188-million manufacturing plant in China and will be investing $88 million in a Life Science Center located near the Nantong site. The plant will produce drugs for China's Essential Drug list to meet the growing demand for medicines in the country.

Regulation

- The Indian Government is set to disband its National Pharmaceutical Pricing Authority. The move will stop the procedure by which drugs labeled as "essential medicines" are automatically subjected to price controls.
- Mylan says it is working to finalize a settlement with the US government regarding Medicaid reimbursements of the EpiPen. West Virginia Attorney General Patrick Morrisey has urged federal and state officials to reject the settlement offer.

For links to original press releases, visit the online version of the article at: http://tmm.txp.to/1016/business

A False Economy

There is a constant drive in the industry to reduce costs, but quality doesn't come cheap, and inexpensive supplies can prove a poor bargain.

By Sven Stegemann

Over the past few decades, the industry has increasingly focused on cost cutting, particularly in the procurement of materials, such as excipients. Often, the choice is made to use the cheapest supplier possible with an assumption that there is no difference between commodity items. However, as much as companies wish it would, quality doesn't come at just any price. Saving money nearly always compromises on quality, perhaps through reduced auditing or reduced analytical controls at the supplier company, which can be detrimental given that excipients are a critical input variable for assuring the quality of the final drug product.

The problem partly stems from the fragmentation of the industry and so-called "management by objectives." Senior individuals in procurement are often under pressure to reduce costs in order to meet their department's objectives, which leads to a strong temptation to consider only cost rather than the full value that quality materials and a good supplier will offer to the rest of the business. Big pharma companies frequently tell me that one of the best locations for outsourcing is India, to which I could reply that, at 323 employees, India's drug regulator is around 2 percent the size of the US FDA's and its authority is limited to new drugs. Quality and safety concerns have led the FDA to ban a number of suppliers and manufacturing sites in India and China in recent years, which is also a blow to the reputations of companies using these suppliers.

It may surprise you to know that many companies do not trust their suppliers – I have heard of pharma companies keeping enormous quantities of stock material because they don't trust their suppliers to deliver on time. So why are they using that supplier at all?

The relationship between a supplier and a pharma company should be a long term one and a good supplier will do more than simply supply you with products. If I ask for 100 million capsules, for example, there are two ways the supplier can react. They can put the capsules in a carton and ship them to me. Or a supplier with a more holistic view on the customer relation will provide the capsules as part of a collaborative effort, assuring that they are on-time, shipped and traced under the required conditions for their supplies, in addition to tracking whether the capsules run on the filling machines as expected.

A good supplier will have knowledge and expertise about their specific excipient, component or service, and considers shared responsibility for the customer success as well. For example, suppliers can help customers to improve manufacturing efficiencies by examining how the excipients or capsules supplied run on customer machines, and how yield can be improved. A yield of 90 percent means that 10 percent of a batch is being destroyed. If your supplier will collaborate with you to get, for example, a 97 percent yield or higher, profits will rise accordingly.

Another area where suppliers can (or must in my opinion) provide invaluable assistance is in regulatory matters. Regulators across the globe have different requirements, so you need to know what materials can be used in each region and what certificates and data are required. Is an excipient or capsule suitable for all markets? Are there specific regulations that you need to be aware of in the market you are considering? This is information that a good supplier can provide. In addition, drug manufacturer have to provide certification and proof of compliance with the existing regulations, such as audit reports of suppliers, TSE/BSE

certificates, as well as data on traceability of the raw materials and analytics. If you are working with a supplier that can smooth this process, or deal with certain queries from regulators proactively on your behalf, it can be a huge benefit.

Finally, I believe it is important to find a supplier who is looking to the future. Manufacturing is not static, and nor is manufacturing sciences. Process Analytical Technologies (PAT), continuous processing, Quality by Design (QbD) and other initiatives taken over the past decade are silently and fundamentally changing pharmaceutical manufacturing; we must prepare for change. Responsible suppliers are already working on the next generation of their excipients to ensure higher performance criteria, functionality and six sigma levels. Moreover, incorporating extra features and functionality, such as enteric properties into capsules address drug delivery challenges, can also significantly reduce manufacturing complexity and hence manufacturing costs.

It's all too easy for those in procurement to miss the wood for the trees – too focused on the budget constraints of their own department, they forget that quality materials and strong relationships with suppliers can have a significant positive impact on the business as a whole.

Sven Stegemann is Director of Pharmaceutical Business Development at Capsugel, Bornem, Belgium

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

Serial Indecision

Serialization deadlines are nigh – and a number of companies are falling behind. Part of the problem is that there are too many solutions available. Where do you start to make a decision?

By Jean-Luc Lasne, Business Development & Alliance Director at Adents International, France.

2016 is a pivotal year for serialization in the pharma industry. Serialization requirements are already in place in South Korea, China and Saudi Arabia, and the deadlines are fast approaching for the US (2017) and Europe (2019). Time is short. Is your serialization strategy in place? Have you selected your solution provider? Have you started to make the necessary changes to your packaging lines? A general urgency is pervading the industry, but many key decision makers have told me that they are finding it difficult to identify the right solution. And the profusion of products now available means the task is getting harder by the day.

Recently, I met with the head of engineering of a contract manufacturing company who was in the process of researching and evaluating track and trace solutions. He started the discussion by saying, "This is a market of dream weavers." It struck me as a very apt comment. There are indeed many solutions to choose from, and whether they prove sweet dreams or lingering nightmares isn't always difficult to assess.

Many serialization technologies are proprietary solutions developed by companies that have traditionally focused on inspection systems. Serialization may seem like a natural progression for such companies, but in some cases solutions have been developed opportunistically by piling on layers of features and software as customer and regulatory requirements have evolved. As a starting point, let us look at how serialization has evolved:

- The first phase of serialization was to print and register/record a string of characters and a Data Matrix 2D-barcode onto the drug carton.
- The second phase was to print and register/record data that vary from one carton to another. It required the printing device and camera to be fast enough to handle new data for each carton.
- The third phase was to develop software to manage the serialization process locally on conveyors. Such conveyors soon became mark and verify machines dedicated to securing the printing process on the packaging line. Suppliers saw a clear opportunity to add value into these machines by embedding software that generates, transmits, checks and captures unique codes, as well as ejecting drug cartons in instances of defect.
- The fourth phase was to connect several mark and verify machines to a central server to store line data at plant level and to exchange data with the organization-wide IT infrastructure.

This current phase is what I call a bottom-up approach because it addresses related needs individually, starting with the existing production environment. In the short term, this approach is passable, but its reactionary nature means it is more patchwork than progressive,

which calls into question whether such a solution will be fit for future requirements. Serialization solutions must be flexible enough to cope with the needs of the future. For example, although coding systems, such as GS1, IFA and the Health Industry Bar Code Standard have standardized barcoding specifications, they are not harmonized. There will be a time, in the not-so-distant future when all serialization systems will need to be able to "play nice" with each other under one overarching regulatory umbrella, which means that companies currently incorporating serialization into their production lines need to be looking for systems that will be universally compatible.

At the moment, each regulator specifies their own data pattern, but the choice of the coding system is up to the drug manufacturer (or the member state within the EU-regulated area). Most, but not all, select the GS1 standard; Germany, Austria, China and a few US manufacturers are notable exceptions. Serialized codes can be either imported or generated on site, and there are several methods to generate unique codes (random or algorithmic). Each Marketing Authorization (MA) holder can also add new requests to the previous pattern, which allows for additional, more customized information to be logged, stored and shared, and request a specific format for the serialized batch data export file.

What does all of this mean? It means that pharmaceutical manufacturers and contract packagers must be able to set-up, exchange and store thousands of data format combinations over time – a process that requires flexible, configurable tools that can generate and exchange massive volumes of data, all while managing manufacturing processes in real time. Many companies are not prepared for the complexity that serialization involves and tend to favor vendors who have previously supplied them with relevant machinery to, for example, print batch data on drug

"Serialization is often more complex than companies first realize."

packs. This is an easy and convenient approach, but it shouldn't prevent you from looking at other options too. On the hardware front, serialization is relatively straightforward – nowadays, all machines can mark and verify 2D codes securely. The more complex part is the software and rolling out a serialization solution is a large-scale, global issue unto itself. For some vendors with a wide portfolio of equipment, however, serialization is just another column in their product portfolio. In my view, it is better to find a true expert who focuses only on serialization – they will be dedicated to the cause because, quite simply, their livelihood depends on it.

Ideally, I advise users to look for software that is specifically designed for global serialization. Obviously, given the approaching deadlines, you need to consider deployment lead times and changeover efficiency, but don't forget about the future – find out about how easy it is to implement changes and upgrades to meet future requirements. And most importantly of all, when in discussion with any vendor about a serialization solution always ask for proof of the claims they make – to make sure you're not just falling into a woven dream.

Open Your Mind

Open innovation is more than just the latest pharma industry buzzword. Done right, it can help overcome funding challenges and accelerate discovery across the board.

By Jackie Hunter, Chief Executive Officer of Stratified Medical, UK.

Open innovation is something everyone is talking about, but what does it really mean? To me, open innovation is more than open access. Open innovation is recognizing that in a world of expanding data and shrinking budgets, collaboration is a necessity, not a choice. It means proactively managing your ideas and your intellectual property, so that if you decide not to act upon them, they are available for other people to progress – through an open access approach or a pre-competitive collaboration, for example. The important thing is that we do not lose all of the wonderful ideas scientists come up with, but drive them forward in the most appropriate way.

The Innovative Medicines Initiative has been a very good example of open innovation in Europe, bringing together a number of companies to fund a range of pre-competitive projects with academia and small companies. Another great example in the UK is the Structural Genomics Consortium in Oxford, a public–private partnership between 13 organizations, including big pharma, government and nonprofit funders in the UK and Canada to create new tools for studying epigenetics and kinase pathways.

The rise in open innovation is intertwined with that other buzzword of modern biology – big data. Terabytes – or even petabytes – of data are being gathered every day from sequencing, electrophysiology and electron microscopy. Big data allows us to integrate data all the way from basic cellular processes to whole organism approaches, and so accelerate our understanding of some of the basic mechanisms of life. There is no shortage of data, and analytical tools exist to convert data into actionable information. However, many individuals or companies will not be able to leverage the power of that data on their own. Instead, they will need to collaborate much more widely to combine and make use of data in new ways. Open innovation also opens the possibility of a crowd-sourcing approach. By using open source platforms to make data available to larger groups of scientists or even the public, we could tap into the power of the crowd to mine information that would otherwise lie fallow for lack of resources to analyze it.

Though open innovation is a popular idea, there is some reluctance to embrace it in practice. Many organizations have simply rebranded their traditional partnership as being "open innovation", but to me it's not the same thing. Traditional partnerships tend to be transactional, with defined members and end points, while open innovation has a much more collaborative ethos. Of course, there is the understandable fear that someone might steal your big idea and leave you out in the cold. But I think the more successful examples people see, the more that fear will subside.

Ultimately, we have more good ideas and great scientists than we have the resources to provide funding for; open innovation and collaboration means we can do more with the same amount of money. More importantly, I feel passionately that getting our best and brightest scientists – whether in industry or academia – working together is one of the most successful ways to drive innovation and speed translation into the societal and economic benefits that we are all striving for.

This article was originally published in The Translational Scientist (https://thetranslationalscientist.com/), a sister publication to The Medicine Maker.

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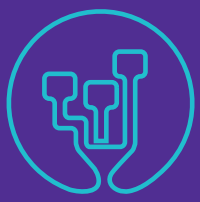

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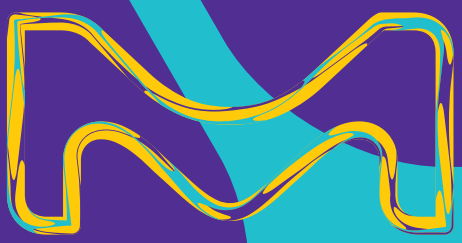

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The Power of Plants

Inexpensive to produce, easy to scale-up and store – plant-based vaccines could boost access to medicines in the developing world.

By Kathleen Hefferon, Department of Food Sciences, Cornell University, New York, USA,

Vaccines made in plants? The concept may sound a little outlandish, but the basic principle is simple: to produce vaccines and other pharmaceutical proteins in food crops such as tomatoes, potatoes or bananas. Studies have shown that eating these vaccine-producing plants can elicit a mucosal immune response.

One of the key driving forces behind the research and development of plant-made vaccines is the lack of access to medicines (both financially and geographically) of much of the world's rural poor. While the Western world takes the control of infectious diseases for granted, cholera, rotavirus, malaria, and many others continue to be major killers of children under five in developing countries.

As a result, much effort has gone into the generation of novel vaccine production platforms with the potential to address the needs of the world's poor. Vaccines generated in plants are inexpensive to produce, easy to scale up and can be maintained at room temperature for prolonged periods of time. Plants also eliminate the risk of contamination by human pathogens, yet can undergo post-translational modifications similar to their conventionally produced vaccine counterparts. Plant-made vaccines originated among a few research groups at a handful of universities across the globe, but they are now becoming a reality.

The first plant-made vaccine to undergo human clinical trials was designed to protect against Hepatitis B virus. This vaccine was initially generated in transgenic potato tubers, which were then fed (raw) to individual volunteers. The researchers found a marked increase in antibody titer against the virus in patients who ate the transgenic potatoes – and demonstrated the first proof-of-concept that vaccines generated and delivered in this fashion could elicit a strong mucosal immune response (1).

Since then, a number of pharmaceuticals have been produced for oral delivery using transgenic plant technologies. Most noteworthy is the glucocerebrosidase (GCD) enzyme for treatment of Gaucher disease. An Israeli company, Protalix, is able to produce GCD at a fraction of the cost of its conventionally made counterpart, using carrot suspension cells.

Vaccines and pharmaceuticals have also been produced from expression vectors based upon plant viruses. Recombinant plant viruses are able to rapidly generate high yields of pharmaceutical proteins, whilst circumventing public concern over genetically modified plants. The Canadian company Medicago, for example, has used a plant virus to express pandemic influenza virus vaccine rapidly and in large quantities. Other plant viruses have been used to generate microbicides to HIV, and even a personalized vaccine to non-Hodgkin lymphoma.

The recent Ebola epidemic in West Africa brought plant virus expression vectors to the forefront once again. Two monoclonal antibodies developed by Mapp Biopharmaceuticals have been generated using a tobacco plant-based production system and have been administered to several patients with Ebola (2).

Plant viruses have also found a role in cancer medicine – as vehicles for tumor homing and immunotherapy. When injected into a cancer patient, empty plant virus-like particles have been shown to navigate and accumulate within solid tumors. Once lodged within these tumors, the virus is able to elicit a highly localized immune response, which blocks tumor progression. This appears to be accomplished by activating quiescent neutrophils, which in turn secrete cytokines and stimulate T-lymphocytes to attack the tumor cells. Nontoxic and biodegradable, these plant viruses could act alone or in conjunction with a payload carried on the surface, or within the virus particle itself, to eliminate and prevent the recurrence of several cancers (3).

Over the past decade, I believe that plants will continue to gain momentum as a novel platform for pharmaceutical production. The fact that the vast majority of patents are held by universities or publicly funded research institutes makes for an accessible intellectual property landscape. And new developments, such as the use of plant viruses to block solid tumor progression, are confirming plant-based pharmaceuticals as "one to watch" in the coming years.

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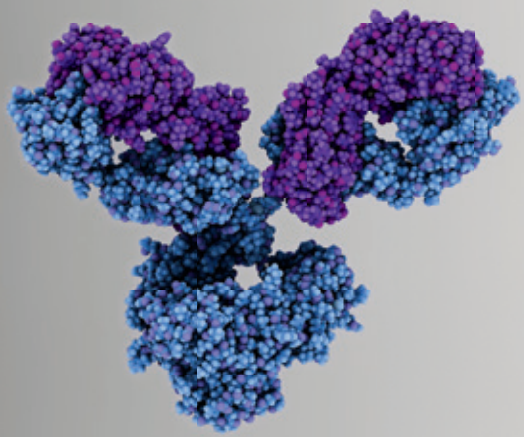

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Protein A: a Question of Affinity

Is there a future for Protein A in affinity chromatography? Some believe not, but others point to the long-established benefits of Protein A resins and the developments and advances that continue to be made in the field.

Scientists and process engineers have been discussing potential alternatives to Protein A for some time – and debating whether or not antibody manufacturers will still be using Protein A at all in the next 20 years. Some see the costs of affinity chromatography and Protein A as a hindrance, but there is little question that it gets the job done. Given that Protein A is the result of millions of years of evolution, is it even possible to synthesize something better?

Affinity chromatography is used in the vast majority of antibody processes, and is used increasingly in processes for antibody fragments. It is generally the first step of the purification train where the goal is to remove the majority of contaminants from harvested cell culture fluid and to concentrate the product before any subsequent purification and polishing steps.

Here, Jonathan Royce, BioProcess Senior Product Manager of Antibody Affinity Resins at GE Healthcare, considers how trends and challenges in affinity chromatography are driving innovation in the field.

Some believe that Protein A will be replaced in the future – do you agree?

I have heard many people talking about the quest for the "holy grail" that will replace Protein A, but I believe that Protein A is the grail! We've been using Protein A for decades and it has a selectivity that is hard to top thanks to natural selection. Protein A is a naturally occurring protein that exists on a specific strain of bacteria – the bacteria has developed its own defense system against an antibody immune response over millions of years of evolution. In addition, over the last 50 years, scientists have used engineering skills to provide other benefits to Protein A based affinity chromatography. Synthesizing something that can compare with that kind of development is always going to be difficult, especially when there is still interest and effort in maintaining developmental momentum. I believe that Protein A will continue to have a dominant role for a very long time.

In general, Protein A resins have not become more expensive from generation to generation, and are ultimately providing better process economies to end users as time goes on. For example, a good article was recently published by scientists from Amgen (1) examining the entire marketplace for Protein A resin. The article showed that, if you look at the development of Protein A resins over time, there is a steady improvement in their productivity, which ultimately leads to improvements in the cost structure for the end user.

Importantly, Protein A is not the only aspect of affinity chromatography that continues to improve – we are also seeing developments in hardware in terms of automation and sanitary design, as well as efforts to demystify the task of packing columns reliably.

What are the alternatives to affinity chromatography and how do they compare?

There are many alternatives to affinity chromatography out there; just as an example, some companies use two-phase separation, which creates a phase-separation barrier between an aqueous phase and a non-aqueous phase, and then concentrates the antibody into one of those two phases. It is also possible to perform precipitation of antibodies and there are certainly people who have developed processes that use traditional chromatography without an affinity step.

All of these have been tested and they are all functional from a technical standpoint, but I don't believe they provide the same levels of simplicity, yield and purity as affinity chromatography. The one downside of affinity chromatography and Protein A is that it can appear to be expensive compared with other chromatographic steps. The ligands themselves are recombinant proteins and the process to produce them is complex. However, if you sit down and calculate the costs of the technology and what you gain in terms of savings in process development, high yields and reduced time to market, I think most people will agree that affinity chromatography is actually cost effective.

What important trends have you noted in the affinity field?

The general trend over the last two decades has been a steady push to increase the capacity of affinity resins. Traditionally, it is fair to say that affinity resin has lagged behind ion exchange and other types of resins that rely more on chemical interactions in terms of capacity (or how much mass of antibody or antibody fragments can bind per liter of resin used). This reduced capacity stems from two factors that limit the diffusion of antibodies into the resins: i) the ligand used is quite large compared with ion exchange, and ii) the binding of affinity ligands to target molecules is relatively strong. Nevertheless, significant progress has been made in boosting the capacity of affinity resins, so now scientists are turning their attention to the process itself: how can we move from a traditional batch process to a continuous or semi-continuous capture step? Rather than processing one batch at a time with a relatively large installation of equipment and resin, it's possible to shrink the equipment and columns, and to use more frequently: continuous processing. This is one area that we are examining in great detail at GE Healthcare – in terms of both equipment and resin.

"Another growing trend is the search for affinity resins that are more alkali-stable."

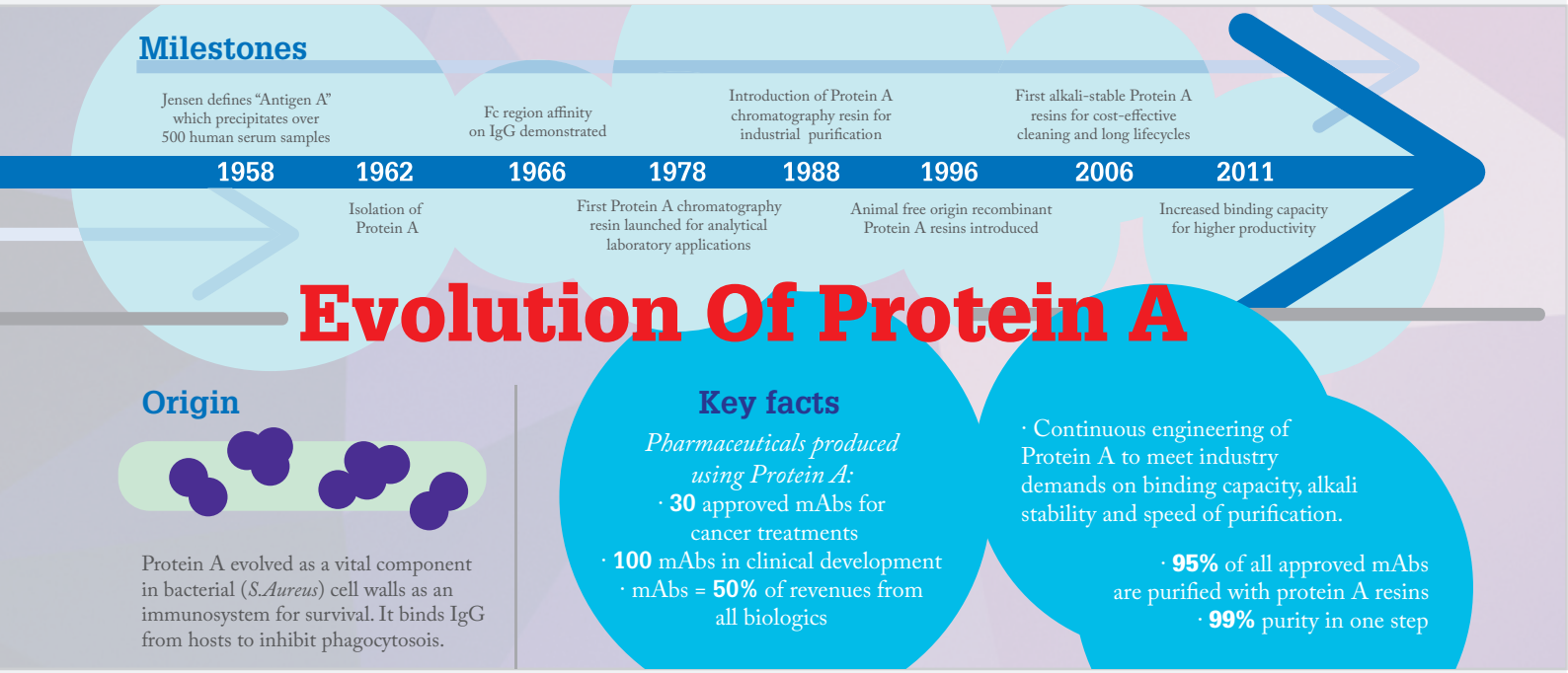
Another growing trend is the search for affinity resins that are more alkali-stable. Why? Because we want to clean chromatography resins with relatively high concentrations of sodium hydroxide to remove proteins left on the resin and control bioburden. Today, we have affinity ligands that are stable at concentrations of 0.1–0.5 M, but there is a desire to push stability further; ion exchange resins are usually cleaned using 0.5–1 M sodium hydroxide. If affinity resins were developed that could withstand the harsh chemicals being used on subsequent steps, it would simplify how people manage clean-in-place (CIP) solutions. Perhaps another important advance in the industry is the development of pre-packed chromatography, which seeing growing interest in the industry. Users rely on vendors to provide ready-to-use columns that can be discarded at the end of their useable life.

Looking at the world of antibodies in general, I would say that the industry is seeing diversification of the antibody pipeline. Fragments have become more popular and represent a larger proportion of earlier clinical phases than they did 10 years ago. Fragments, by their very nature, lack the Fc region of the antibody to which Protein A binds, leading to the development of other affinity solutions; for example, Protein L and Protein G based resins, which bind other moieties of the antibody structure.

How are the growing number of antibody drug conjugates and bispecific antibodies affecting purification processes?

The purification of antibody for an ADC isn't very different to that for a typical antibody – and a lot of the ADCs in development or that have been launched are based on antibodies that were developed 10 or 20 years ago. However, there are certainly challenges after conjugation, the most common being how to separate the ADC from free antibodies or cytotoxin. The separation is made more challenging because you are working with cytotoxic agents under special conditions. There is a lot of focus on how to perform these separations in a closed manner, with minimal handling of the raw materials, which has led to a strong preference for single-use technologies.

In some cases people have solved some of these separation challenges by using filtration steps, but they can also be solved by using scavenging resins that are built into pre-packed chromatography columns or by using membrane absorber technology. There is no standard solution yet, which means that each project requires customization, but in time I think we will



see a greater level of standardization as the industry begins to understand what works reliably for these complex products.

Bispecific antibodies have a different set of challenges because they are very much like fragments and their structures can be diverse. There are more than 40 different bispecific antibody structures under development today. Some can be addressed with Protein A, some with other kinds of ligands, while others require individual purification processes based on orthogonal techniques, where process development must be performed from scratch each time.

There is no question in my mind that bispecifics will create a larger market for customized purification solutions, where vendors develop a specific resin for a specific molecule, such as customized versions of Protein A resins or even customized chromatography techniques. As an example, GE has previously developed a specific variant of one of our Protein A resins for a customer who had a unique, patented bispecific antibody structure. With an increasing number of these kinds of products coming through company pipelines, it will be crucial for resin manufacturers and antibody manufacturers to work together.

What are your tips for choosing the best purification equipment and processes?

It is important to try to think ahead – to anticipate how manufacturing will look in the future. What is your company's plan for manufacturing? How do you want your process to look? You need to understand what equipment you already have available, what needs to be acquired to implement the process, and what the ultimate goal of the manufacturing process is. Is it going to run at maximum productivity? Do you need to minimize the investment in terms of capital equipment? Do you want to minimize the amount of time spent on process development from project to project? If you spend quality time thinking about these questions then your answers will establish much of the criteria for choosing the right solution.

One thing that is easy to underestimate, if you are not already working this way, is the value of a platform process. Nearly all of the major antibody manufacturers have settled on a platform process that they leverage from project to project. And there is a very good reason for this: when you have a platform, you do not have to constantly repeat process development each time a molecule comes into your portfolio. A platform will probably never be 100 percent optimized, but it will be good enough to satisfy the needs of most projects – and the benefits of having a standardized set of operations will generally outweigh the incremental gains you could obtain by optimizing every individual process.

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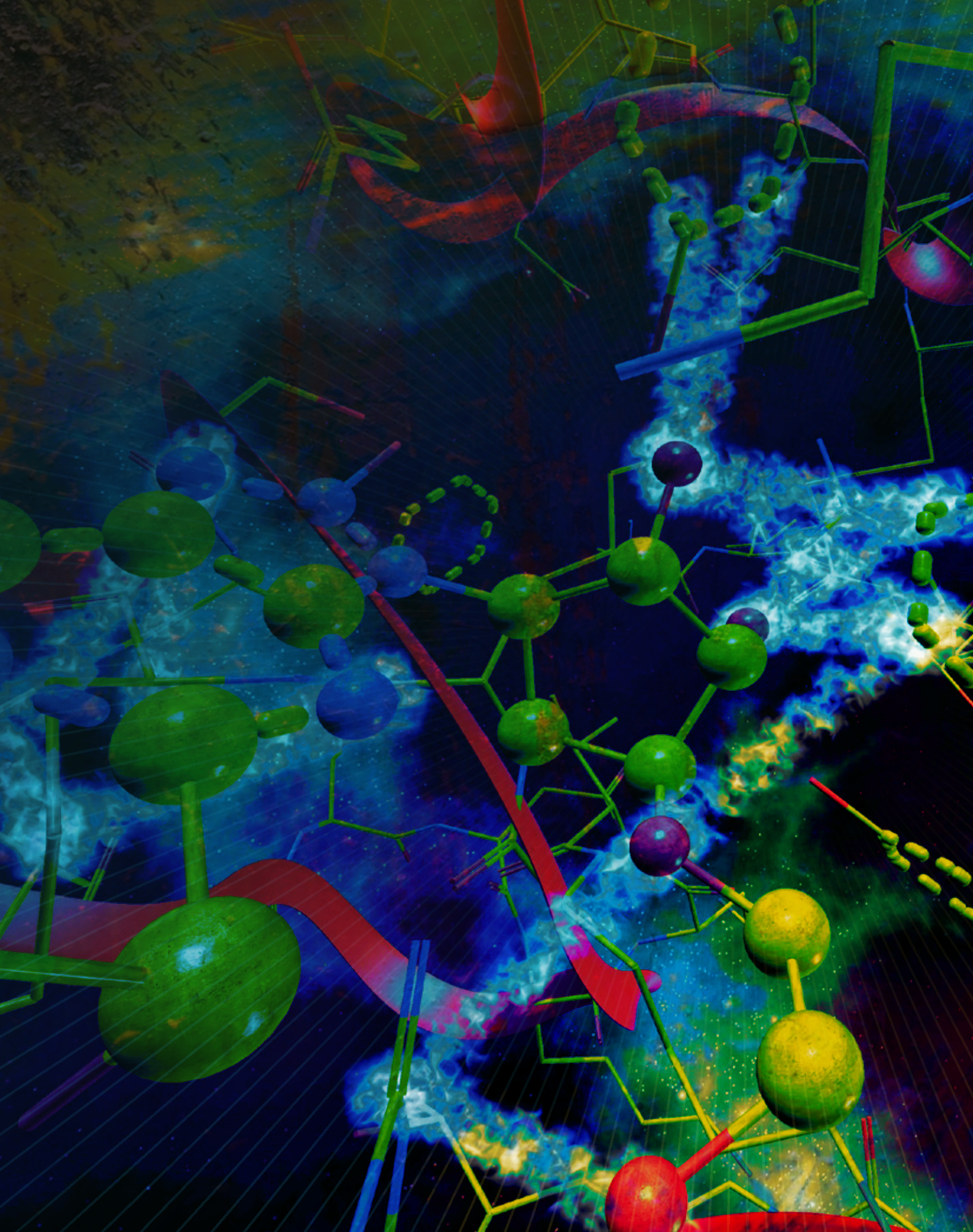


REACHING INTO A NEW REALITY

The IT and video gaming industries have helped refine augmented reality and virtual reality technologies. Can the pharma industry take them to a whole new level to improve the manufacture of medicines?

By Stephanie Sutton

Mention the words "virtual reality" (VR) or "augmented reality" (AR) to anyone in the pharma industry and most will admit that the technologies are "cool". But at the same time there is a general feeling that the technologies are gimmicks that will see little use outside of marketing campaigns.

Interestingly, healthcare is one of the few sectors that has been using VR and AR for many years in very practical and inspiring applications. For example, VR has been used to provide patient therapies for pain reduction, post-traumatic stress syndrome, phobias, and even for teaching people to walk again. VR and AR are also being explored to help train neurosurgeons, with Duke University in North Carolina experimenting with using AR to assist in delicate brain surgery.

The big question for The Medicine Maker? Will AR and VR have an impact on pharma manufacturing? Over the next few pages, experts share their vision of AR or VR, and how it could be used to make a difference in drug development and manufacturing.

HARNESSING AUGMENTED REALITY

How Google Glass inspired hands-free access to information for process engineers.

By Angelo Stracquatanio

There is no doubt that VR and AR are hot buzz words that capture one's imagination. Because of this, some may wonder if there is substance behind the flash – and if there is substance, is it viable and can it be used within the industry? For these technologies to cross the bridge from consumer gaming to productive tools, it is important to provide practical applications that people can see true value in. I'm particularly focused on AR within pharma manufacturing and R&D, and have seen first hand the impact these technologies are having on the industry.

I'm an enterprise mobile developer by background but I've been building or leading teams that create iPad applications and mobile applications for Fortune 500 companies industries throughout my career. In 2013, Google Glass was released – and I was inspired. Google Glass is an AR headset that allows users to perform a variety of functions with voice commands (or even the blink of an eye). I liked the hands-free access approach and I saw potential for "something", though at the time I wasn't quite sure what that something was – it was just a raw device with no practical enterprise software.

Several months later, I was having a conversation with a friend, who works as a process engineer in the biopharma industry. We were talking about the things that go wrong in your day job and she explained how she always had to drive over an hour to a facility to troubleshoot problems and how people often used incorrect or out-of-date paper-based procedures, which meant she would have to stay late to fill out paperwork. Given all the communication technologies at our disposal today, I was pretty shocked that this still happens in business. As the conversation moved on, I started talking about Google Glass (which was by now collecting dust on my desk) and suddenly it dawned on us both at the same time that access to critical, hands-free information could be very valuable to process engineers. If you sit behind a computer all day, you always have information at your fingertips, but when you're working in a lab or manufacturing facility, it's a different story. Some companies use tablets but these aren't always convenient depending on the location – and they don't provide hands-free information.

It was a crucial "aha" moment for both of us – and after some thought we decided to try and make a business out of it. The company we formed is called Apprentice Field Suite. We came up with three core ways that Google Glass could be used by biopharma process engineers:

i. See what I see. Can somebody else, somewhere else in the world, see through my eyes to coach me through something and provide assistance? Or train me in a new technique?
ii. Paperless procedures. Can I see a procedure in the glasses so that I can work with two hands?
iii. Safety and data collection. Can I look at equipment and collect different, non-digital types of information and collate them into a digital format?

Early challenges

I was the one who built the applications, but of course it wasn't

Augmented Versus Virtual Reality

Virtual reality

VR headsets or glasses – examples of which include the Oculus Rift, Samsung Gear VR and PlayStation VR – completely block out the real world and instead, as the name suggest, present you with a virtual reality created by software. You could be walking up a mountain, playing a game on a battlefield, or standing in a surgical room. VR can also artificially create sensory experiences such as touch, hearing and, in some cases, even smell (the curious among you may wish to look up the Nosulus Rift). A large number of VR headsets and glasses are in development.

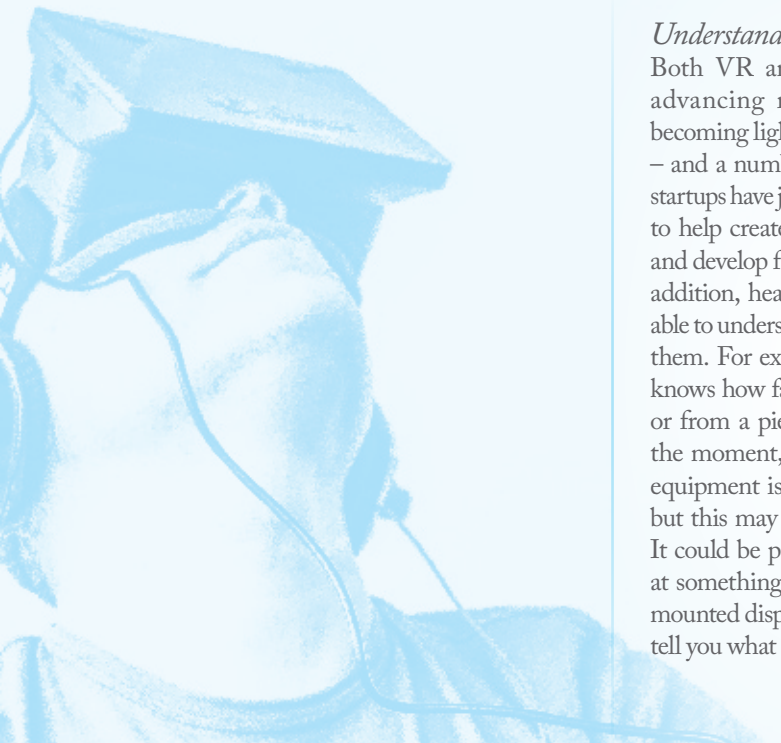
Augmented reality

Whereas VR replaces the real world with a virtual one, AR shows you the real world supplemented by virtual elements – Pokemon Go is the most famous and ubiquitous example at present and allows users to discover cartoon critters in a live view of the real world. Thousands of smartphone apps using AR exist, from games to interactive maps to translation tools. Headsets and glasses have also been developed. Google Glass, which has now been discontinued, is perhaps the most well known, but there are dozens of alternatives available. Some companies are developing AR headsets for workers that provide data visualization, for example.

as straightforward as I'd imagined at the outset. We decided to target biopharma specifically since my partner knew the industry inside out, but the regulatory hurdles when working in biopharma are immense and it was a shock to my system! I can't even begin to explain how long it took to get everything compliant. I needed to ensure that everything could be tracked, logged and validated. We also had to look at the challenges of deployment from an IT perspective. How do you stop someone from walking out of the building with the glasses? Or taking them to inappropriate places within a building? We worked with a partner to develop IT management software that uses a concept called geofencing, which allows you to control what the device can do depending on where it's physically located.

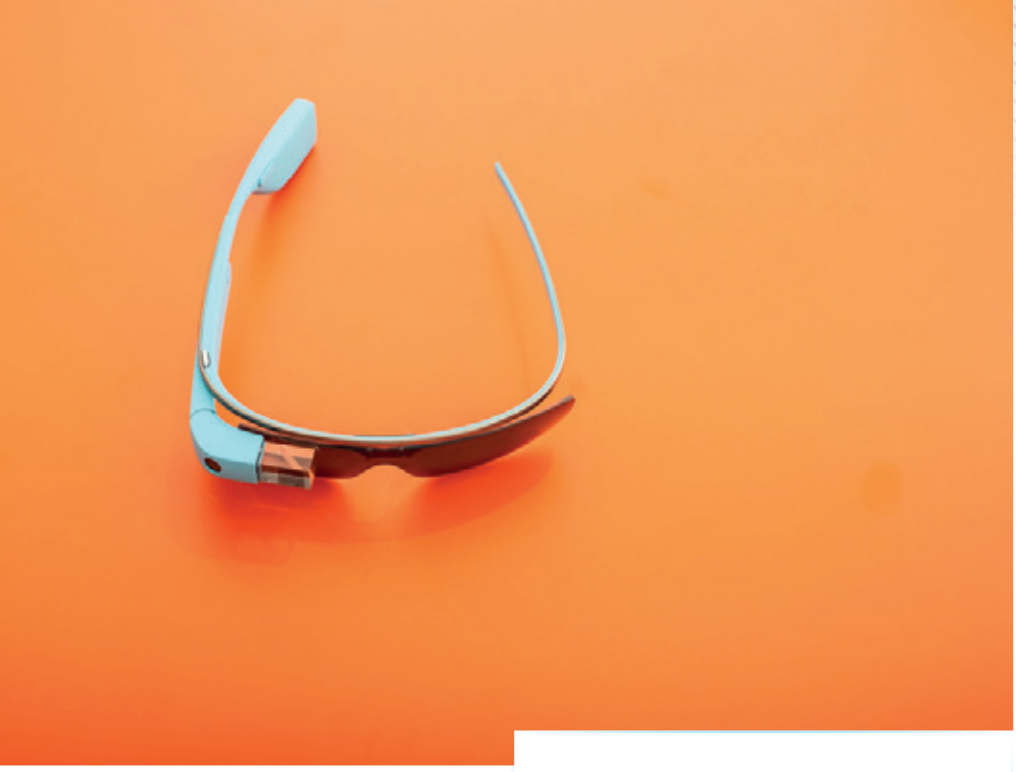
There were also challenges on the hardware front. At first, I was developing everything for Google Glass, which had its limitations (and was eventually discontinued), so I had to start looking at other glasses. I decided then, early on, that it was critically important for our solutions to be completely hardware agnostic. Thankfully, there were many other technologies to choose from that were just as comfortable as Google Glass. Just five years ago, AR glasses were very clunky – it was like putting a 10-pound weight on your face. Today, the display and hardware has been miniaturized to make the glasses wearable and comfortable, and the image quality is great – all of which makes the technology more viable.

Crucially, however, the applications we had devised made sense to people in industry. We spoke to people during development and tested a prototype in a laboratory environment. Everything seemed to work and it seemed to be useful to people in biopharma – very good news! The next step was the fingernail-biting



Understanding the world

Both VR and AR headsets are advancing rapidly in terms of becoming lighter and less expensive – and a number of companies and startups have jumped into the market to help create pricing competition and develop further applications. In addition, headsets are increasingly able to understand the world around them. For example, the HoloLens knows how far you are from a wall or from a piece of equipment. At the moment, it can't tell what the equipment is without a QR code, but this may change in the future. It could be possible to simply look at something and have your head-mounted display (HMD) or glasses tell you what it is.



launch. We saw potential for the technology and believed it could be useful, but how would people in such a conservative industry react to a new technology?

We launched at the Interphex 2015 trade show in New York and were voted Best New Product at the show. It was a relief to see that the technology really did resonate with the industry. I spoke to a lot of people at Interphex who had actually bought a Google Glass, but like me didn't really know what to do with it. When you develop a turnkey solution though, suddenly Google Glass and the idea of AR becomes more than just a flashy, gaming device. Since the launch, I've given a lot of demos about the technology and it's very interesting to see how people react. Before the start of a demo, people don't actually "get it". I throw out words like "smartglasses" and "enhanced telepresence" but although people nod they don't really understand – until they put a headset on. As soon as they see and experience AR, the tone of the meeting completely changes. It's quite magical. I really believe in the potential of the technology, and it's very rewarding when other people suddenly see the value too.

"We saw potential for the technology and believed it could be useful, but how would people in such a conservative industry react?"

Real world use

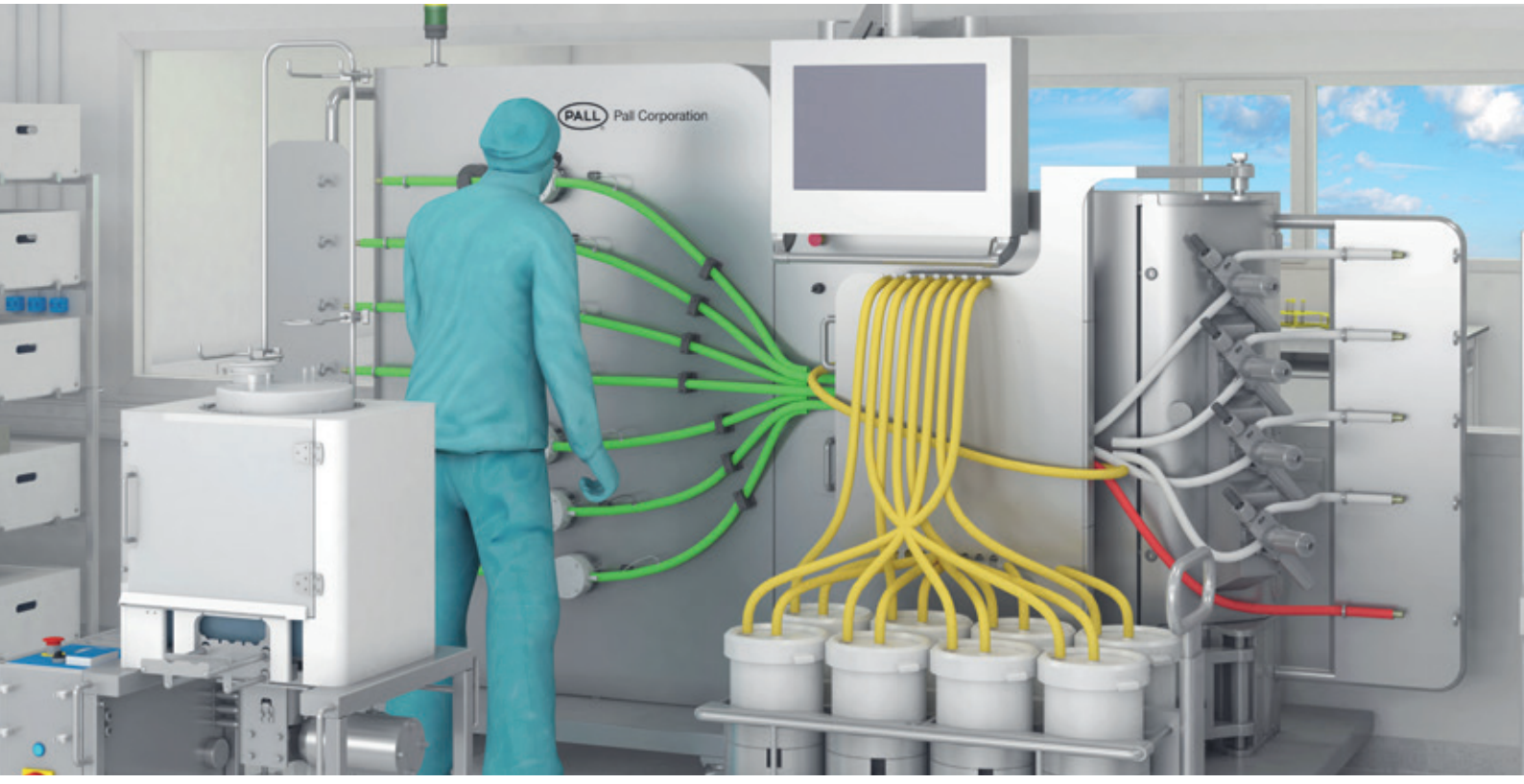
Our clients are mostly large global pharma manufacturers, biotechs, CMOs and equipment manufacturers. Our team assists them with our AR tools in areas touching operations, engineering and R&D. Some of what we do is available out-of-the-box, while some elements require custom integration. One of our customers, Catalent, is using the technology to allow remote experts to see what an individual operator or engineer is seeing in real time. For a company with a large global presence, it is particularly useful as it helps save on travel expenses and service contracts – a very obvious and immediate return on investment. The person wearing the headset can continue to work hands-free, and the expert can even draw on their field of view to show which connection needs to be removed or to highlight if a specific button needs to be pressed, for example. This sort of application is also extremely useful if ever you need vendor advice about purchased equipment.

A top five biopharma company, which I can't name, is using our technology to access user manuals hands free. A worker can walk up to a piece of equipment that has a QR code on it, scan the code, and the work instructions pop up in the glasses. The instructions are tailored to the person wearing the glasses and the piece of equipment they are looking at, as part of the verification process with our IT controls. Batch records also appear in the glasses and values can be recorded via voice; for example, the worker may need to record a value of 50 ml for the sample; all they need to do is to speak the value and it will be saved in their system.

Some of our other customers have been utilizing our technology in maintenance and facilities, as well as in quality assurance, safety and packaging. Training is another popular application of the technology. Managers can also look at reports to see how long each step is taking, what engineers were working on and if there were any deviations from procedures, which can help refine instructions.

All of these applications are actually very simple, but when you implement them on a practical level it can really change the way people work.

Angelo Stracquatanio is Co-Founder at Apprentice Field Suite.



VIRTUAL FACILITY DESIGN

A facility can be planned on paper, but will it "feel" right and function as expected? Virtual reality can provide a sneak peak into potential problems by allowing you to walk around facilities before they have been built.

By Ian Sellick

It can be disorientating when you first experience VR, since what your eyes are telling you and what your body is doing are out of phase with one another. It does, however, have a definite "wow" effect. VR is a fully immersive experience and I think the potential applications are fascinating. In 2015, at the BioProcess International trade show, we used VR to show visitors how our cell therapy bioreactors worked. However, VR can do far more than draw people to a booth.

The story of how Pall became interested in VR is a winding one. We produce a wide range of content in terms of operator manuals and technical training, and we also produce video training manuals for a lot of our equipment in cases where it is hard to describe what to do, but very easy to show people what to do. We are always looking for new ways to do this. A lot of the training items and videos that we produce are made in our facility in Belgium, and the team there started to tinker with 3D modeling in their spare time. They became very passionate about the potential and eventually some of them left to set up a startup marketing company called OUAT! – and Pall became their first contract. We gave them the remit of showing how our cell therapy bioreactors worked and how they fit into a facility.

OUAT! created a 3D virtual world that users could interact with. It was early days for VR and to be honest the optics weren't great, but we presented it at the BioProcess International show

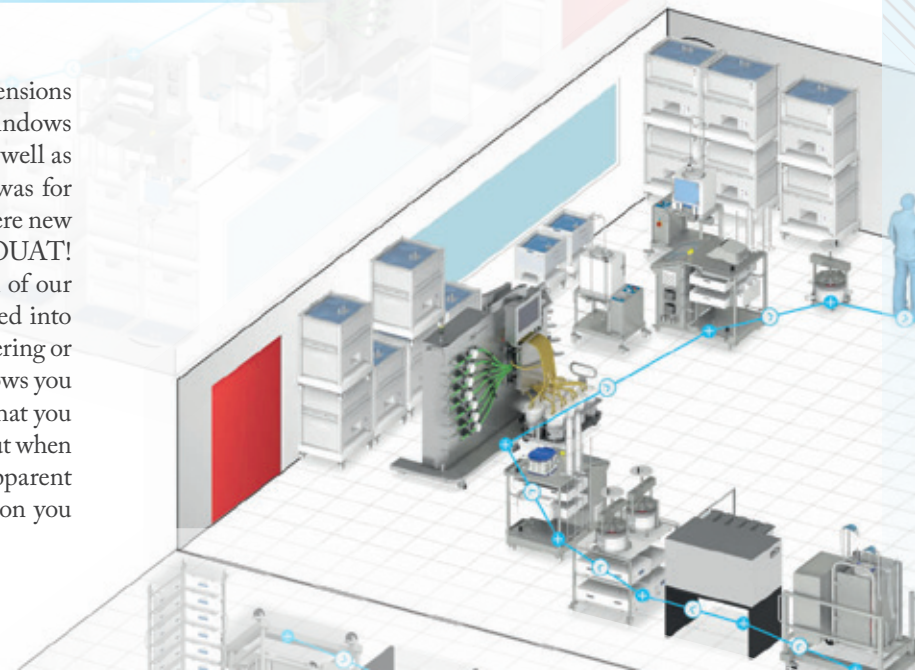
anyway – and people loved it. Visitors interested in cell and gene therapy could walk around a virtual facility and look at where the bioreactors were installed and interact with them – albeit in a fairly modest way. Based on the response and feedback from people at the show, we were inspired as to what we could do with VR next. In particular, we wanted to do more than just show people something; we wanted to make it more applicable and personalized so that users could be fully immersed.

We went back to OUAT! and the timing was perfect since OUAT! was designing HakoBio – a process and cleanroom planner. They were able to create a virtual space for users to build a laboratory or a whole facility. Users could set the dimensions and then look at where the doors went, where the windows went, where the utility collections would be housed, as well as where other architectural features might be. The aim was for users to either recreate existing facilities (to evaluate where new technology might be placed) or to create new facilities. OUAT! also created 3D virtual models of a very large selection of our portfolio of products that could be dragged and dropped into their designs. It's something you can do in a lot of engineering or architectural modeling programs, of course, but VR allows you to switch from a design point of view to a virtual view that you can walk around. It may sound like a gimmick to some, but when you walk around a facility, sometimes things become apparent that you couldn't see on the plan; for example, a location you thought was appropriate for a piece of equipment might not be right. Building a facility is expensive and you want to get it right – being able to walk around and see how it goes together early on can make a big difference.

At the moment, I consider all of this phase I – I think that VR can be taken a step further so that users can actually interact with objects, such as pushing buttons and opening doors. This may sound futuristic, but the technology is already there in the world of video games. If you are interacting with something in the virtual world then you need some kind of tactile feel, as well as position indicators for hands. We are keeping a close watch on the technology. As well as being used for marketing and facility planning, VR could also be invaluable for training operators in the correct use of equipment. Eventually, I'd love to see the integration of computational fluid dynamics so that users can see the behavior of liquids that are being processed through the system. Eventually, maybe we will be able to look at the microscopic level and visualize what is happening in, for example, the interactions of multiple molecules with chromatography resin. We can already perform static modeling with 3D molecular design software, but being able to watch it will add a new dimension – and could drastically change the field.

"In particular, we wanted to do more than just show people something; we wanted to make it more applicable and personalized."

Ian Sellick is Director of Marketing at Pall Life Sciences.



A New Angle for Marketing

By Nicolas Vertommen, Marketing Architect of OUAT!

Matthieu Egloff and I are the co-founders of OUAT! – a life sciences marketing company with a large focus on creative digital experiences, including 3D modeling and virtual/augmented reality. Mathieu has a background in bioengineering, while my background is in marketing – and through the combination of this expertise, we aim to deliver simple and integrated digital tools. Both of us used to work for ATMI Life Sciences (now Pall).

At ATMI, Matthieu and I were responsible for the marketing and management of innovative bioreactors. At this time we were becoming frustrated by a key aspect of our jobs: we were selling very advanced, high-tech equipment, but our main selling tool was a simple PowerPoint presentation. When selling bioreactors, the same questions come up every time. What kind of footprint does it require? How does it fit with my process? How can I connect it to other equipment? With a PowerPoint presentation, we were only able to represent the labs of customers using squares, rectangles and circles, which isn't the most effective method of understanding how new equipment will fit into a facility, or to help customers to imagine their lab of the future, so we started to experiment with other methods, such as 3D technology. 3D is incredibly useful because you can show off things that cannot normally be seen; for example, you can project the customer inside of a future environment or show them the inside of a product. And of course, VR can take this even further...

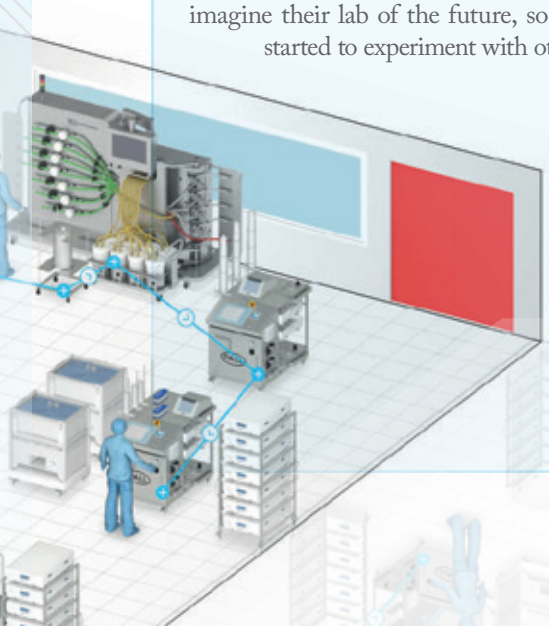
When we started OAUT!, we met someone who had nothing to do with the biopharma industry – who showed us VR. Anyone who has tried VR knows that the first time you experience it is a big "wow" moment. We fell in love with it and we knew it could be a powerful tool for biopharma applications. In Belgium, where we are based, there is a huge buzz around VR, which has helped us a lot – our work is actually now sponsored by the Microsoft Innovation Centre in Brussels.

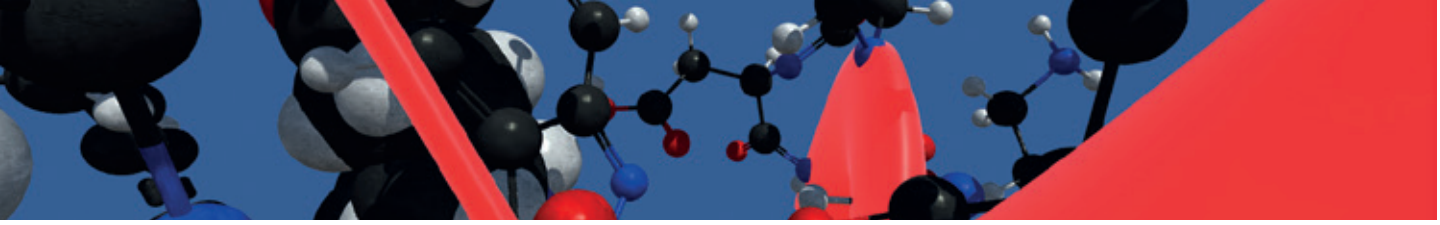
As Ian explained on page 33, we have combined VR with motion-capture technology to enable users to interact with a computer-simulated cell therapy facility. This project required huge efforts in the design of the facility and we rapidly started to think about a solution that would make this simple. This is how we created HakoBio – a web-based platform that can be used to create conceptual designs for processes. Bioproduction equipment is modeled in 3D and you can drag and drop products into your pre-configured room. IKEA actually does a similar thing with interior design. It's very simple, but incredibly useful – and it's amazing to think that there is nothing similar for the biopharma industry. One big pharma company recently told us that they still use pen and paper when thinking about their future labs. The other option is to work with large engineering agencies. We can't replace such agencies of course, but we can be the link between the pen and paper, and the highly technical tools used by engineers – and support the conceptual design of processes and labs.

Pall isn't the only company we are working with (customers include Sanofi Pasteur and Roche Diagnostics) – and one of the really fascinating aspects of my job is seeing the different ways in which people interpret and then implement the technology. For example, in recent work for a global company, we were interacting with people from Europe but they were building a new facility in the US. The team was multidisciplinary, comprising people from many different regions, and one of the main draws of the technology for them was the ability to easily collaborate because everyone could share the design and experience it. We've also worked with a CMO who wanted to use our platform to showcase their current and future capabilities, and demonstrate how flexible their infrastructures were.

Today we are expanding the database of 3D models to additional bioprocess equipment – and discussions with vendors are progressing well. To further open the field of possibilities and opportunities with our tool, we are also partnering with a company that is active in the capture and management of big data from connected bioprocess equipment. We are investigating how we can leverage the HakoBio platform to visualize and analyze a large amount of data – after all, labs produce a lot of data that can be difficult to visualize and we may be able to help.

Essentially, we're working towards making the concept of industry 4.0 – where you could manage a facility from a desk at home – a (virtual) reality.





ENTERING MOLECULES

Drug designers already use molecular visualization tools to help them with their jobs, but virtual reality can take this to a whole new level – while also making you feel like Tom Cruise.

Jonas Boström is a drug designer based in the Department of Medicinal Chemistry at AstraZeneca in Sweden. He has a Masters in Chemistry from Göteborg University, but has always had a keen interest in computers – which he attributes to the two Commodore 64s of his childhood. At an early age, he learned to program in BASIC and would swap games with friends in the schoolyard. After being introduced to computational chemistry in the late 1990s, he decided it was the perfect fit for combining his love of chemistry and computers.

Boström and his colleagues have developed a molecular visualizer tool called Molecular Rift, which creates a VR environment where users can interact with molecules using hand movements. Boström tells us more.

How did you first get interested in VR?

Ever since I saw Tom Cruise moving objects around in augmented reality in the movie "Minority Report", I've wanted to do something similar, but with molecules. And then a talented student of mine (Magnus Norrby) asked if he could do his master thesis in computer science with me. He was very persistent in wanting to use the latest VR technology: Oculus Rift. After six months of creative hardwork we had developed a VR molecular visualizer: Molecular Rift.

How does Molecular Rift work?

Molecular Rift creates a VR environment using Oculus Rift goggles. Users can interact with molecules through gestures. We like to think of it as the next generation of molecular visualization. It can, for example, be used to view protein–ligand complexes in a new way because drug designers can step inside a protein and be fully immersed. Remember, all molecules ranging from small-molecule drugs such as aspirin to the famous DNA double helix are 3D objects, which drug designers work with on a daily basis. The first version of Molecular Rift was controlled with the gaming sensor Microsoft Kinect v2 (developed for the Xbox One console), but this wasn't ideal since the Kinect is designed to track a whole body rather than fine finger movements. In version two, we implemented the more advanced Leap Motion sensor, which allowed near perfect accuracy in gesture recognition.

What were the early challenges you faced?

One problem was a supposedly straightforward matter: acquiring the actual hardware. We ended up buying a used (and the last one available on the site) Microsoft Kinect v2 from Amazon in the US – and got a friend of a friend to ship it to us in Sweden. The Oculus Rift goggles were also not easy to get hold of. Technically, it was a challenge to work in a Windows environment, which can be quite restrictive for programmers. We use a few software development kits in Molecular Rift, and it wasn't always easy to get the different versions to play with each other. But, Magnus is a computer whiz kid so all technical challenges seemed trivial to solve. They most probably were not…

> *"We like to think of it as the next generation of molecular visualization."*

What stage is the project at now – and what comes next?

We've just got the code to work with the new consumer version of Oculus Rift, and the open-source Rift version has just been modified to work with the HTC Vive headset by a collaborator in New Zealand. High on my wish list now is the ability to visualize molecular surfaces and manipulate structures. I'm also a believer in the potential of voice recognition. I tried Amazon Echo (Alexa) a while ago and was stunned by how accurate it was. It would be cool to use that with Molecular Rift.

You've also started a new company EduChemVR…

EduChemVR is a company that Magnus and I just started. When I studied chemistry in the late nineties, the lecture halls were full of students but today chemistry is a rather unpopular university subject – seen as dry and dull. I think that's because chemistry is abstract and difficult to understand. Enter EduChemVR. We aim to take a lead in gamifying chemistry education by making VR smartphone apps to engage students and inspire further studies. With EduChemVR smartphone apps and cheap Google Cardboard, teachers and students can be teleported into virtual worlds of atoms and molecules. Molecular Rift requires a high-

quality computer and the Oculus Rift goggles, making it relatively pricey. By using Google Cardboard technology, however, we believe that we can reach anyone everywhere; from VR enthusiasts in the western world to impoverished school kids in developing countries. Our vision is to make chemistry the coolest subject to learn.

What are your thoughts on the future of virtual reality in the pharma industry?

A tough question. The pharma industry is facing many challenges right now and it is too easy to down-prioritize IT investments. However, I do know that it is being used in quite a few public relations projects, such as to show how drugs actually work. And some companies are also investing in CAVEs – cave automatic virtual environments – but CAVEs are not the height of VR technology today in drug discovery.

There are a number of VR-skeptics out there. For example, a frequent question we often hear regarding our work is, "Is Molecular Rift more useful than traditional molecular visualizers?" A virtual reality experience is famously indescribable. We can write and talk about all the amazing things one can experience until the sun goes down, but until you get people to try VR for themselves it's just words. Many people don't realize just how cool and useful VR is until they try it. It's like when Morpheus says to Neo in the classic Matrix movie: "Unfortunately, no one can be told what the Matrix is. You have to see it for yourself."

The Machine Maker

As well as potentially changing the way things are done in pharma and biopharma manufacturing, could VR be useful in the design of manufacturing equipment? Bausch+Ströbel, a supplier of pharmaceutical packaging machines, created a "Virtual Reality Center" in 2011. We spoke with Thomas Bühler, sales group leader at Bausch+Ströbel, and Tobias Hörner, who is in charge of the company's VR system, to get their take on how VR is revolutionizing machine making.

How did Bausch+Ströbel get started with using VR?

The automotive and aviation industries can be considered the pioneers of VR technology. Other industries, including the special machine building industry, have been using VR in marketing for quite some time already so it was only natural that it piqued the interest of several Bausch+Ströbel employees as we specialize in building machines! Some of our salespeople, engineers and students analyzed possible applications and the results of the analysis and a presentation of the system convinced our management of the potential benefits.

How is VR used within the center?

We are using VR in a number of ways, including: virtual mock-up studies, design reviews, safety studies, ergonomic studies, failure mode effects analysis, training, machine redesign assessments, computer-aided engineering and air flow visualization

We also use the technology for marketing purposes, such as giving customer or trade show presentations. It can also be used for assessing animated processes.

How did employees react to the technology at the outset?

When we introduced the VR system, our customers and staff were quite curious. At the beginning, it was strange for everybody to work with a machine mock-up that they could not touch – it was a very different sensory experience. Still, the spatial view and fine details of the machine model were convincing and it wasn't long before curiosity transformed into continued support of the technology. We've been working with VR for a few years now and there are benefits for our customers and us.

Benefits for customers:

- VR technology saves time in project work.
- Customers can get involved in early project planning.
- Our processes and work flows are more efficient and transparent to the customers.
- We found that the fault rate in virtual mock-ups was zero percent.
- Applying VR technology has been cheaper than any alternative technologies.

Benefits for our company:

- We can use the system to demonstrate machines that we have already built. As we offer a wide range of machinery, we often do not have real machines to show to potential customers.
- We can involve our customers more closely in the product development process, increasing their acceptance of our technological solutions.
- New design features can be tested and implemented much faster.

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Process Operator
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40–43
Podifying Cleanroom Processes
Are the days of the traditional cleanroom numbered as the industry begins to consider more mobile cleanrooms solutions, including self-contained pods? Maik Jornitz gives his view.

Podifying Cleanroom Processes

With the advent of mobile, flexible cleanroom solutions that can be moved to wherever medicines are needed, are traditional cleanroom infrastructures about to become obsolete?

With Maik Jornitz

Containment is a key word in our industry and cleanrooms are an essential part of pharma manufacturing. As discussed in a previous issue of The Medicine Maker (1), the technology behind the modern day cleanroom dates back to the 1970s and there is doubt as to whether such static infrastructure is best suited for the needs of today's industry, where flexibility is key. One of the main problems with traditional cleanrooms relates to scale up. Extending a cleanroom is a time-consuming and messy affair – and every time you scale up, you have to re-qualify the cleanroom infrastructure, which disrupts the manufacturing process. As soon as you start moving traditional gypsum walls, other problems can also become apparent. When speaking to peers in the industry, people have often said to me, "We opened up a cleanroom wall and found mold." Contaminations like this are a hidden fact in the industry. Many cleanrooms are simply too outdated to fix – no matter how much money you throw at them. I don't believe that cleanroom infrastructure should be a sunk cost. Many infrastructures are mothballed at the end of a product's lifecycle because the investments would be too high to refurbish or modify the facility to meet the new processing criteria. This wouldn't be a problem if we had autonomous, flexible cleanrooms that could either be repurposed for another application or transferred to another site – even another country.

Meet the "POD"

In 2011, I was introduced to the concept of independent, prefabricated cleanroom "PODs" that can be used inside of a facility in place of a traditional cleanroom. A modular and moveable cleanroom is not a unique concept

as such – a number of companies have built container-based facilities that can be connected to a standard facility, but once interconnected these systems become just as inflexible as a traditional facility system. Pods and container-based cleanroom units differ mainly in the assembly – the pods are independent cleanroom units, which require a shell building, but container-based systems are interconnected units, which ultimately assemble to a free-standing facility.

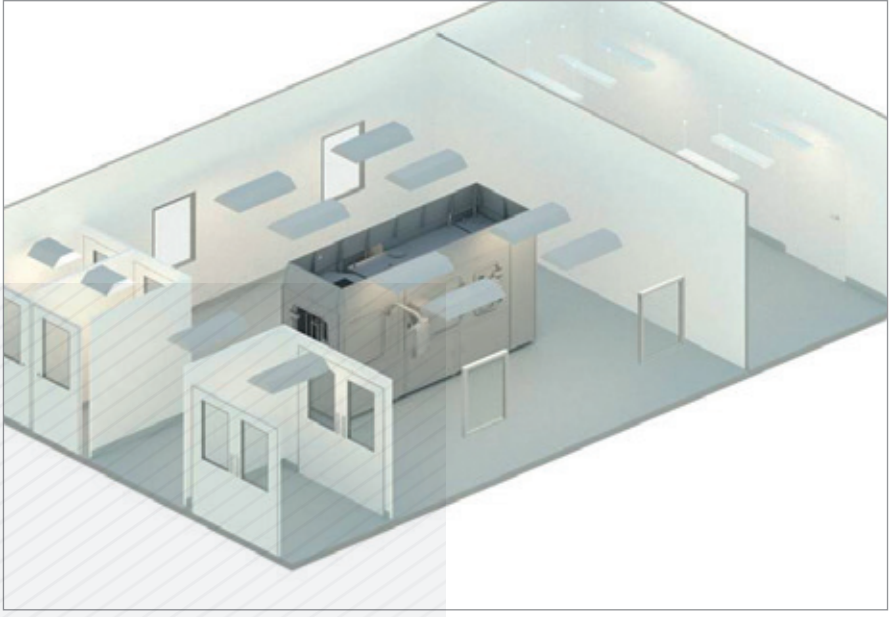
"Importantly, the pods are self-contained, so if there is contamination in one then the others will be unaffected."

The pods I was shown each had their own air-handling and control units, as well as fire suppression system. Like a normal cleanroom, there was a gowning area and a cleanroom area. Depending on the situation, the pods can be "docked" to corridors within an existing facility, be delivered with a corridor pod or have the corridor included in the pod structure. Importantly, the pods are self-contained, so if there is contamination in one then the others will be unaffected. If necessary, they can be decontaminated via vaporized hydrogen peroxide, which may be important – particularly given the contamination discussions relating to minute mouse virus (MMV) and other contaminants. Moreover, self-containment makes it easier to scale the cleanroom area up and down and thus achieve capacity flexing.

The concept of the pod was devised by a team working with individual patient samples, who needed to scale up their cleanroom area but were fed up with the need to revalidate traditional cleanroom areas whenever they expanded their processing space. They wanted to make a cleanroom "box" that could be placed inside a shell building, and which can then be multiplied without interrupting existing processes. When I saw the outcome – cleanroom pods – I realized that they were ideal for single-use process unit operations or small-scale filling systems. The pod forms a self-contained, mobile containment around processing units – you no longer need just a single-use unit operation, but can implement the unit into an environment with similar flexibility.

Pods vs the traditional cleanroom

Being inspired by a technology is one thing, but making it work on a practical level in the pharma industry is a challenge. The early pods I saw were good, but certainly not perfect and improvement via understanding industry needs was essential. If compact cleanroom technology is to make a mark on the industry then it must be robust and associated with quality – we want the technology to be considered a mobile device rather than a rotary phone. To this end, it is important to



Mobility Means Flexibility

By Stephanie Sutton

Constructing a traditional cleanroom tends to be associated with a number of necessary evils – mainly the time required for construction and the fact that companies invest in one room, in a fixed location. If the facility is decommissioned then the cleanroom environment can't be redeployed elsewhere. Today's modern facilities are usually designed with flexibility in mind; for example, it is possible to build flexible rooms with fixed utility stations in the ceilings and walls that allow processes to be moved around, but there are limits to how flexible hard infrastructure can be. To address this problem, a number of vendors offer construction services in terms of modular and portable cleanrooms.

Modular cleanrooms

Modular cleanrooms can be seen as a more flexible option than traditional cleanrooms because they can be installed quickly, with little onsite disruption, and relocated or upgraded as needs and capacities change. They are used as both temporary and permanent cleanroom facilities – often being used to extend an existing cleanroom. Modular cleanrooms must sit within a shell facility and are made of prefabricated wall and ceiling panels. The main benefits of a modular cleanroom is flexibility – a modular cleanroom can be small or large, and easily expanded by adding new panels. A modular cleanroom can also be built around existing equipment and can be relocated elsewhere in the facility – or taken to another facility and re-assembled if required.

Soft and hard walls are available for modular cleanroom construction. Soft walls are not suitable for all cleanroom applications, particularly the most demanding applications, but can be an economical solution for certain projects, such as some medical devices. They are often used to upgrade a specific area. Generally, a soft wall is a clear plastic panel supported by stainless steel frames. Hard walls are rigid and suitable for a wider range of cleanroom classifications.

Portable cleanrooms

The portable cleanroom is constructed offsite and can be moved to wherever required. In some cases, the cleanroom is completely contained – one common method is to build a cleanroom environment inside a shipping container – which negates the need for a shell building and allows the cleanroom to sit, for example, in a carpark. Usually, some site work is required first to prepare for the arrival of the cleanroom. Other portable cleanrooms are designed to sit within shell buildings. In almost all cases, portable cleanrooms are designed for temporary or short term use only. Some of the main users of portable cleanrooms in the pharma industry are small manufacturers who are short on space and need temporary extra capacity. Portable cleanrooms don't have to be purchased – they can also be hired.

use the right materials. Steel, while well established, is too heavy to offer mobility and can rouge over time. The material should be lightweight, but also have the longevity and strength to endure being moved around – we decided to go with aluminium.

In our eyes, the technical challenges of pods have been largely overcome – they are not difficult to design or build, and we believe users will be able to buy these systems off-the-shelf in the future. In addition, industry acceptance, if not demand, of flexible cleanroom technology is rapidly increasing, with a number of vendors now pushing modular cleanroom concepts. One of the biggest obstacles to more widespread implementation is that manufacturing companies tend to focus on cost per square foot – companies want to directly compare the cost per square foot of a pod or other solution to that of a traditional cleanroom, and they fail to fully consider the total cost of ownership. This is something commonly seen with new technologies in the pharma industry – it was the same for single-use process technologies in their early days; companies viewed the ongoing cost of consumable bags as a negative. Slowly, the industry started to realize that although a stainless steel vessel negated the need to buy a bag at around $500 or so, it instead incurred thousands of dollars of cleaning, energy and set-up costs. Once companies became more aware of the hidden costs of stainless steel, the adoption of single-use technology accelerated and today,

single use process technology adoption is commonplace.

The cost per square foot for a podular cleanroom (and often for modular cleanrooms too) is usually higher than for traditional cleanrooms. The value of an alternative to standard cleanroom infrastructure can be seen, however, once you consider the total cost of ownership. When installing a new cleanroom infrastructure, would you prefer a hundred workers at the site for six months, which also involves insurance, supervision, laydown area and potential mess, or five people at a site for a matter of days? We recently installed seven pods at the University of Tennessee in four hours. The most time consuming aspect is interconnecting electrical and supply lines, which takes around three or four days.

The sweet spot for flexibility

Ultimately, whether you choose a standard or flexible cleanroom will depend on your needs. The main benefits of flexible cleanroom technology lie in process-intensified manufacturing applications, when companies are unsure of future demand or are manufacturing multiple products. At the moment, there is a lot of focus on flexible manufacturing in the cell and gene therapy field. These therapies are advancing rapidly but there is some confusion over how best to manufacture them – certainly, with one batch per patient, they don't fit with the traditional manufacturing model. A big question with these therapies is: should manufacture be centralized or decentralized? At the moment, companies want manufacturing capacities fast but there is a reluctance to spend time and money on hard infrastructure when things may change. With pods or other flexible solutions, manufacturing can first be centralized but if it needs to be decentralized later then it's no problem – just take the pods out and move them.

In my opinion, if your plans are subject to change then it's far better to have a flexible manufacturing solution that you can move around and adapt as you please. At the moment, many aspects of pharma manufacturing are changing – there is a huge drive for smaller footprints and intensification – particularly with continuous bioprocessing being adopted – and this allows the industry to consider more compressed cleanroom areas. For example, given that we now have concentrated media which can be fed directly into the stream via single-use systems, companies in the future may no longer need a media prep step. If you're using pods then you can just refit your media prep pod into something else or move it elsewhere. The idea of pod farming is something that was raised by a client of ours recently. What if everything could be manufactured in clusters of pods? Instead of having a huge facility could you share a plant with other tenants and share the admin, quality management and quality assurance costs?

"If your plans are subject to change then it's far better to have a flexible manufacturing solution that you can move around and adapt as you please."

I think some of the most exciting ideas for the future of flexible manufacturing will come from the end users in the industry. This year, Pfizer received a Facility of the Year award for the Equipment Innovation category – and our pods played a part in that. We are in a consortium with Pfizer and GEA to design and build a portable manufacturing environment for continuous oral solid dosage production. It can be shipped to any location to get medicines to patients when and where they are needed.

Given my expectations for the future of flexible cleanrooms, is there still a place for traditional cleanrooms too? Absolutely. Traditional cleanrooms are not going away and will be invaluable for large-scale projects – you can't fit 15,000-liter bioreactors in one of our pods! The trend is moving towards continuous production with smaller equipment, but this won't be suitable for all medicines. Some companies will continue to need huge stainless steel infrastructure. Once again, I visit the analogy of single-use technology. Over the years, many have asked if we will still need stainless steel in the future – yes, we will. Single-use adoption started slow, but is growing exponentially and will continue to do well because of its flexibility – and we expect to see the same trend with mobile and flexible cleanroom solutions; a hesitant adoption, which starts becoming a fast one. But this doesn't mean that other technologies will go the way of the dinosaurs. More flexible technologies, such as podular and modular options, will simply give companies more tools to work with to improve drug manufacturing.

This article is based on an interview with Maik Jornitz, CEO and President, G-Con Manufacturing, Inc., College Station, Texas, USA.

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The Potential Pitfalls of Price Controls
With pharma companies increasingly focusing on specialty medicines, drug prices are rising beyond the means of governments, patients and payers. Price controls may seem like an easy solution, but the quickest fixes are not always the best in the long term.

The Potential Pitfalls of Price Controls

As the public demands more be done to address ever-increasing drug prices, government-mandated price controls may seem like the answer. But the evidence suggests that legislation could hamper innovation and potentially have a negative effect on patient health outcomes.

By George A. Chressanthis

Drug pricing and patient affordability of medicines have been major political points of the 2016 US presidential election. Government-imposed price controls on older generic drugs (1), limits on patient out-of-pocket drug expenses (2), and tighter limits on pharmaceutical pricing overall were major policy positions for both candidates. The drug industry has also been cast in a very negative light during this political cycle. The Pharmaceutical Research and Manufacturer of America (PhRMA) noted that calls to directly control drug prices would "turn back the clock on medical innovation", restrict patient access to medicines and - according to comments from some health economists – have little effect on stemming drug prices (3).

The issue of high drug prices is also a hot topic in the medical literature among healthcare professionals, especially given the growth of personalized medicines and new specialty medicines (3-9). The high cost of cancer medications, in particular, has caused oncologists to reevaluate the value framework for these drugs (10). Despite the ongoing discussions, no long-term "solution" on drug pricing has emerged that has broad consensus among public policy officials, politicians, patient advocacy groups, medical and health service researchers, drug industry representatives, and healthcare professionals. But invariably, the "quick and easy fix" option of price controls is raised. While this option may seem publicly appealing, it is important to consider thoroughly the relationship between drug price controls and patient health outcomes.

Drug price controls, according to microeconomic theory, are hypothesized to affect patient health outcomes in two ways:

- Price controls diminish the diffusion of new drug technologies. Assuming that new drug technologies contribute to advances in patient health, the result would be eventual lower health outcomes.
- Price controls decrease incentives for pharma investments in R&D and drug innovation output, which in turn result in eventual lower health outcomes.

The effects of the first relationship are relatively short-term, whereas the effects of the second relationship are seen over the long-term. But what does published evidence have say about these relationships?

Price incentives do matter

Empirical research shows that the shift in pharma R&D to focus on specialty medicines has been driven partly by the greater freedom companies have to price these medicines, particularly when there are few, if any, competing products (11). In addition, there is much evidence to show that a country's pricing environment impacts the diffusion of new drug technologies. The IMS Institute for Healthcare Informatics has forecast that "in 2020 the use of new medicines, introduced in the prior 10 years, will represent 0.1 percent of volumes in 'pharmerging' markets, compared to 2–3 percent in developed markets" (12). The difference in drug utilization will likely result from a combination of both relative price and income effects across markets. Naturally, however, pharma companies will seek diffusion of new drug technology in countries where they can reap higher prices to help pay for R&D (13, 14). For example, companies often choose to avoid countries in Europe with lower prices and stringent price controls, and introduce fewer new drugs after entering a price-controlled market (15). The existence of parallel imports further delays new product

launches, meaning that price control policies in one country can have spillover effects in other countries (15).

Another large study across 15 countries found negative new drug price elasticities in the -0.75 to -1.1 range, as well as positive (but small) cross-price new drug quantity effects with respect to old drug pricing (16). (Drug price elasticity estimates into the elastic range – greater than 1 in absolute value – suggests that the diffusion of new drug technology will be hampered by an environment that creates higher price sensitivity.) This study is unique and interesting as it also captured the effects that promoting older drugs have on new drugs – promoting older drugs can have a significant negative impact on new drug market share.

A second study examining 642 new drugs in 76 countries, from 1983 to 2002, found a robust relationship between patent and price regulation effects, and the diffusion of new drugs – in the manner predicted by economic theory (17). That is to say, patents and price controls create a balancing act of conflicting forces. On one hand, patents create government-protected IP monopoly power, thereby rewarding companies taking risks – though at the expense of higher prices. On the other hand, direct price controls lower drug prices but also reduce rewards for innovation. There is no "right" answer here, but rather which trade-off society wishes to accept.

The policy path chosen in the US on this issue is one that tries to balance the trade-off between providing incentives needed for innovation, while at the same time minimizing the negative effects patents create for society – through the creation of patents of limited duration (to make it easier for generic and biosimilar drugs to enter the market) and government subsidies that protect drug access for at-risk groups (Medicare Part D and Medicaid, for example). Whether this approach is better than the more direct approach of regulating drug pricing as done throughout much of Western Europe or Canada depends on the criteria used to evaluate the outcome.

Lastly, another large study done over time and across selected Organization for Economic Cooperation and Development countries found that higher US brand prices relative to other countries contributed to faster diffusion of new drug technologies – but also higher spending per capita on prescription drugs (18).

Overall, the literature demonstrates what economics 101 teaches us – incentives do matter.

Innovation benefits health

What about the more complicated relationship of price controls and pharmaceutical R&D? This is a more indirect relationship and involves a chain of effects. The first link in the chain is the relationship between drug pricing and pharma R&D investment – and a long line of research has shown that drug pricing does impact R&D. The second link is the relationship between R&D and patient health outcomes.

Pharma companies are increasingly focusing on high-cost, specialty medicines – especially those classified as orphan drugs (19) – which require higher incentives to compensate for the added cost and risk involved in development (20). Evidence of the impact of the US's Orphan Drug Act of 1983 suggests that the incentives enacted through this legislation have boosted the number of drugs for rare diseases. More than 500 drugs for orphan diseases have been developed since the act passed in the US alone, with other countries adopting similar orphan drug programs (21).

Numerous empirical studies show a strong connection between the enactment of price controls and reductions in pharmaceutical R&D investment – leading to decreases in new drug innovation (22, 23). Another study estimated that a 10 percent decrease in the growth of real drug prices caused an approximate six percent decrease in the growth of R&D intensity (24). A more recent study concluded that enactment of patents and exclusivity provisions, while having pros and cons as a policy approach (e.g., the establishment of monopoly drug pricing), still play a dominant role in incentivizing biopharmaceutical R&D (25). Overall, there is an established body of academic literature that establishes the relationship between drug pricing and price controls, and pharma R&D investment and drug innovation.

But what of the second link in the chain – the relationship between the adverse effects of R&D development and drug innovation, and patient health outcomes? Here too, the literature can guide us. The most direct study is one that estimated the effect of real (inflation-adjusted) price declines from price controls on reductions in R&D investment, and then in turn, on life-years lost (in millions) (26). Model estimates determined that a 10 percent, 30 percent, and 50 percent decrease in real drug prices from price controls, decreased R&D investment by 5.8 percent, 17.5 percent, and 29.2 percent, and led to life years lost (in millions) of 40.1, 113.5, and 178.8, respectively. This connection to reductions in life-years lost depends on the relationship between the diffusion and utilization of new drug innovation, and patient health. Pharmaceutical innovation was estimated to increase life expectancy by 1.27 years during the period 2000–2009 for 30 developing and high-income countries (27).

Similar studies have been conducted by the same author showing country life expectancy rising alongside pharmaceutical innovation. However, not all empirical studies show a strong relationship between pharmaceutical spending and life expectancy; for example, one study in Canada found no effect between drug spending, and infant mortality and life expectancy at 65 (28). Economic theory may explain how reduced pharmaceutical R&D and lower diffusion of drug innovation could result in lower health outcomes, but the empirical challenges of determining a robust effect amongst all the other factors that can affect life expectancy and/or health

outcomes is a daunting task. While the empirical studies presented here generally show a strong relationship between price controls and patient health outcomes, more research is likely needed to determine the robustness of the effect and its magnitude.

The US and price controls

Given that drug pricing has been a big topic during the US elections, it is possible that the country will see some form of direct drug price controls in the future. Instituting drug price controls would be a policy approach consistent with a populist-oriented Trump presidency. Whether the Republicans in Congress – who now control both chambers and have traditionally voted against such controls – would go along with it remains to be seen. Pressure will be exerted by the progressive wing of the Democratic party, which has gained in influence during this election cycle from the Bernie Sanders run, and will most certainly push for direct government-imposed drug price controls. Yet, the US government already has a number of powerful mechanisms to help control prices. For example, the federal government establishes Medicaid drug pricing based on significant discounts from the best commercial price being offered. It is important to remember that significant market forces affect pricing, from increased branded drug competition and competition from generic entry post-patent expiration (including early patent challenges), to bioequivalent and therapeutic drug substitutions. Concentrated market power is shown to affect drug pricing and utilization by drug wholesalers, large health payers, and dominant pharmacy benefit managers.

What those advocating for drug price controls often fail to recognize is that the pharma industry is undergoing rapid and fundamental changes. The easy disease targets that can be addressed with small-molecule drugs are rapidly vanishing and more incentives, not less, are needed for pharma companies to unlock the solutions to the most challenging unmet medical needs. Complicating the challenge facing drug companies is the fact that both improvements in health outcomes and costs of care will be measuring sticks to determine future rewards from drug innovation. This will be an expensive endeavor, and questions exist as to whether society is willing and able to pay for increases in drug innovation needed to solve these medical challenges – the future is admittedly uncertain.

"Instituting drug price controls would be a policy approach consistent with a populist-oriented Trump presidency."

Various groups have traditionally banded together to advocate against direct drug price controls in the US and to date their efforts have been successful (29). However, the dramatic increases in prices necessary to support drug innovation are straining the coalition. Increasingly, new drugs are being priced beyond the means of both payers and patients. Even for drugs that deliver both extraordinary health outcomes and cost-effectiveness – such as new treatments that cure Hepatitis C and so prevent costly complications – patient access is limited because widespread use would quickly bankrupt healthcare reimbursement systems. At the same time, the current commercial model that companies are using to maintain profitability (mainly through price increases) is clearly unsustainable in the long run (30, 31).

As the public demand that new drugs be more widely available, a complete re-evaluation of the system that determines drug pricing is taking place, with drug price controls being increasingly deemed part of the solution. In light of this, pharma companies must radically re-evaluate the commercial models traditionally used to generate and support the prices of specialty medicines. The shift to focus on specialty medicines means the current commercial model – based on a set of increasingly obsolete market dynamics and less-emphasized drug technology going forward – is rapidly decreasing and will need to be changed. Companies need to be demonstrating improvements in everything they do, along the entire product lifecycle, to produce better health outcomes and lower costs of care. The backlash against drug pricing and greater calls for price controls likely reflects that the industry has not yet effectively delivered on this value-based argument. The good news for the industry is that there is still time for internal changes to strengthen this argument. However, if changes are not made, the politicization of drug pricing and public discontent will mean greater government involvement – with negative effects for the industry and patients. As Milton Friedman, a Nobel Prize-winning economist, once said, "If you put the federal government in charge of the Sahara Desert, in 5 years there'd be a shortage of sand." The empirical evidence presented here suggests that a more heavy-handed approach by the US government to erect price controls will not promote overall social well-being, but will decrease drug innovation needed to address significant unmet medical needs, and adversely affect patient health outcomes.

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The full list of references are be available online: http://tmm.txp.to/1016/chressanthis

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UBM

Pride and Passion

Sitting Down With... Steve Turley, Managing Director for the British and Irish Isles, UCB.

What drew you to the industry?

My degree is in public policy making. My dad was a medic who was very supportive of the pharma industry – which is sadly quite rare – and he suggested that it could be a good industry to build a career in. At first glance, my degree may not seem that relevant to the pharma industry, but as managing director, knowledge of economics and government policies is incredibly beneficial to understand the complexities of healthcare systems, such as how they are funded and how priorities are set.

Why is it rare to find people who support the industry?

If you look at the purchases we make in our everyday lives, most people value the contributions of the companies at the forefront of innovation – just look at how much support a company like Apple receives from its customers, despite selling expensive products! In the pharma industry, our medicines genuinely change people's lives, and yet our society puts so little value in the research and manufacture of those innovations. I find it a strange paradox.

We must never forget that while we are a commercial industry, we also provide real value to people's lives. We shouldn't shy away from the fact that we have to make profits and generate a return for stakeholders and the investment community because that is what allows us to reinvest in the medicines of the future. Having said that, the need to prove value is only going to increase. As an industry, we can't put our heads in the sand and say that it's not our problem. We have to make sure that the products we produce have real value for patients.

What have been your main career milestones?

Moving from a junior role into middle management was a big step for me – I moved into an international job within Roche's global organization based in Basel. Until then, my career had been purely in the UK-based commercial side of the organization. When I moved into my new role, the drug I was focused on was coming to the end of phase III, but about six months later, the drug failed to meet the specified endpoints. It was clear that the problem was with dosing rather than efficacy so the company decided to redo the phase III program.

For me, this meant that rather than being a commercial guy coming in at the end of phase III, I was suddenly at the beginning of phase III. I had to contribute to what the phase III studies should look like; understand what the regulatory processes entailed; how we formed a brand name; how the manufacturing would work; and so on. That four-year stint gave me a huge amount of insight into the R&D, regulatory and filing process. It was fascinating.

You've been with UCB for a year… How are you finding the role?

It's been great on a number of levels! UCB is a nice place to operate. It is a mid-sized company but it doesn't feel hierarchical – the chief executive and executive board are very accessible and have a keen, day-to-day interest in the business. In addition, the patient is very much at the center of what we do. In almost any pharma company headquarters you'll see inspiring mottos about patient value on the walls, but I think there are few companies where those words actually translate on a practical, everyday basis. All at UCB are working hard to bring those words into action.

The company operates in therapy areas that I've worked with in the past and that I'm very passionate about. The big learning curve has been the epilepsy side of the business, but in any new role it's important to bring value as quickly as you can.

"We must never forget that while we are a commercial industry, we also provide real value to people's lives."

You are very passionate about disease-awareness campaigns…

I believe that a healthcare system needs to serve the needs of a broad range of patients. A disease like cancer, for example, receives a great deal of attention – and rightly so, because it has devastating effects on patients and those around them. However, it frustrates me that some other disease areas are relatively neglected.

It's important that diseases such as Parkinson's or epilepsy don't get left behind. There is tremendous pressure on neurological services – they are already under-resourced and more resources are being taken away. Pharma companies need to work with national health agencies to ensure patients get the care they need.

What are your proudest achievements?

One of my personal values is built around the concept of pride, which is about looking back and always asking, can I take pride in what I've done today? Can I take pride in the fact that the decisions I made were based on the right ethics and morals? Can I take pride in the fact that I've supported my people – and looked after my family – as best as I can? For me, it's not about choosing certain moments but being able to say on a daily basis: I'm proud of what I do.

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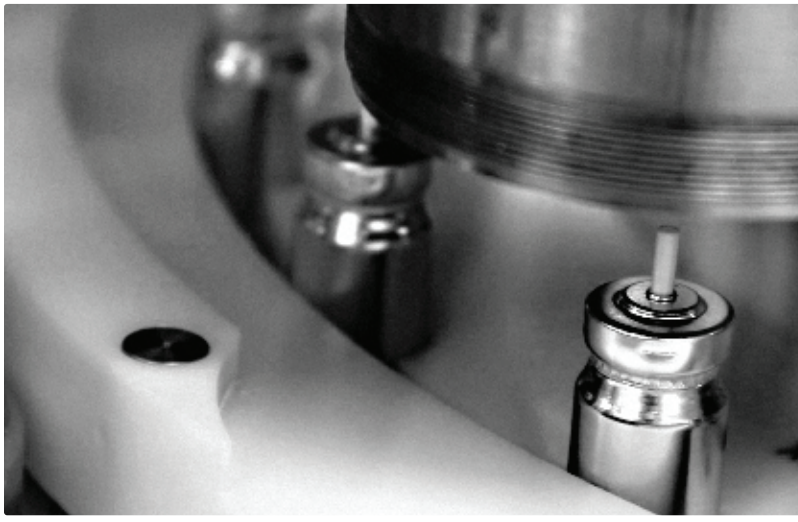

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