FEBRUARY 2017 # 27

the Medicine Maker

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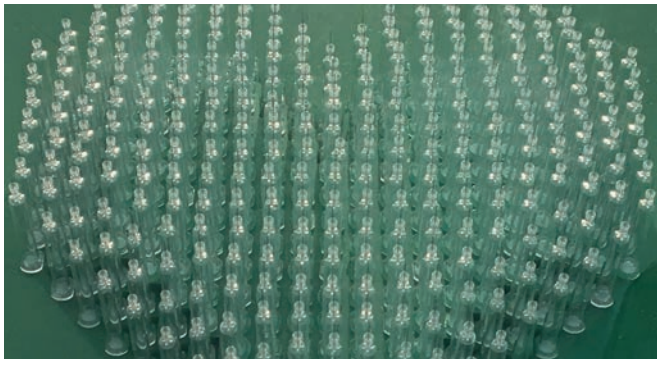
Online this Month

Marketing Myths

Articles about marketing in The Medicine Maker usually discuss pharma marketing tactics, but what about the tactics of contract manufacturing organizations? Elliott Berger from Catalent points out that rather than marketing to the healthcare community, contract manufacturers have to market to pharma businesses – and they need advice too. The marketing field is full this fad and myths – every new technology, app or trend is a "must have" and must be the focus for every contract research, development and manufacturing organization that wants to market its services. In this online article, Berger combats this fad by using another fad: the currently ubiquitous "top 10 list" of anything and everything.

Visit http://tmm.txp.to/0217/berger for Berger's top 10 myths in B2B marketing.



Upfront Extended

This month, two of our Upfront articles feature expanded information on our website.

On page 8, Changing Markets voice their concerns over antibiotic resistant bacteria found in wastewater from pharma plants in India – and more detail is available at *http://tmm.txp.to/0217/changingmarkets*

And on page 9, we get arty and find out why Terumo decided to create an art gallery for a trade show. More information (and images of their display) are available at *http://tmm.txp.to/0217/terumo*

Pressure Cooking Pricing

In mid-February, Marathon Pharmaceuticals announced it would be charging $89,000 per patient per year for Emflaza (deflazacort), which was recently approved by the FDA for Duchenne muscular dystrophy. The decision, however, has caused outrage amongst the public, as well as accusations that the company is abusing the FDA's orphan drug program.
http://tmm.txp.to/0117/marathon

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Do Not Go Gentle Into That Good Night

PhRMA and the ABPI showcase the industry's good side and the science behind the logo

In the last issue of The Medicine Maker, I noted the urgent need for the pharma industry to win back trust and restore its public image. The task also seems to be high on the agenda of Pharmaceutical Research and Manufacturers of America (PhRMA) – at the end of January, it unveiled a substantial advertising campaign called "GoBoldly".

The campaign aims to "salute the sheer will and tenacity of patients and scientists fighting against disease every day" – and PhRMA's first television advertisement is a worthy effort. The ad has clocked up thousands of views on YouTube, and I highly recommend taking a look: http://bit.ly/2lLUXSW. It boasts a movie-trailer feel, and features a voiceover of Dylan Thomas' poem "Do Not Go Gentle Into That Good Night" as well as a stunning piece of music (Solarium by Jonathan B Buchanan). It taps into the human element of drug development – the tireless dedication of scientists who work long hours to prevent patients from slipping into that "good night".

The campaign's dedicated website – www.goboldly.com – includes information about personalized medicines, immunotherapy and genomics, as well as personal stories from patients. PhRMA also intends to convene events across the US to discuss how the current healthcare system can be made to be more responsive to the needs of patients.

Meanwhile in the UK, the Association of the British Pharmaceutical Industry (ABPI) also wants to showcase the industry's good side. And though not quite as dramatic as PhRMA's trailer, the ABPI has created a three-minute film called "Only Just Begun" (http://bit.ly/2lg7GQP) that celebrates the past and present of drug development in the UK with a mixture of historic and present-day imagery. The ABPI has also created a range of online content that aims to demonstrate the value of medicines and vaccines, as well as the pharmaceutical sector's worth to the UK economy.

Comments on YouTube suggest that PhRMA's campaign, in particular, has been very well received. It's a shame then that those efforts have been overshadowed by the media storm around Marathon Pharmaceuticals' pricing of a drug for Duchenne muscular dystrophy. For scientists with an "indomitable will" to cure, how frustrating it must be to watch their industry being tainted by yet another apparent example of corporate greed.

The Medicine Maker remains steadfast in its original mission: to celebrate the best of pharma but also to scrutinize the bad – and we're always open to articles that explore either side of the coin.

Stephanie Sutton
Editor

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

Testing the Water

Pharma is urged to tackle the problem of polluted waste water from manufacturing plants – before antibiotics suffer

Environmental campaigning organization, Changing Markets, recently published a report uncovering widespread antibiotic resistant bacteria in wastewater from pharmaceutical plants in India (1). Pollution from antibiotic manufacture is thought to be a factor in the global spread of drug resistance, alongside excessive consumption of antibiotics in human medicine and their profligate use in livestock rearing. We spoke to the group about why – and how – the industry should address this important environmental issue.

What did your investigation reveal?

Our report exposed the occurrence of resistant bacteria surrounding pharmaceutical manufacturing plants in India, which supply European and US markets. An on-the-ground investigation by the investigative agency, Ecostorm, and subsequent analysis of water samples under the supervision of Mark Holmes from the University of Cambridge found high levels of drug-resistant bacteria at sites in three Indian cities: Hyderabad, New Delhi and Chennai. Out of 34 sites tested, 16 were found to be harboring bacteria resistant to antibiotics.

How widespread is the problem?

This is just the tip of the iceberg. Our research is the equivalent of a "pilot study," but of course more extensive research would be required to establish the full scale of the problem. Pharmaceutical pollution is an emerging issue and even developed regions, such as Europe, could make considerable improvements to their regulatory framework. For example, the European Commission's Strategic Approach to pharmaceuticals in the environment is already more than a year late, which is concerning.

What can be done?

The Review on Antimicrobial Resistance characterized pharmaceutical manufacturing pollution as "a supply chain problem that pharmaceutical companies and their suppliers need to solve together" (2). We couldn't agree more. Pharmaceutical companies have a duty to stamp out pollution throughout the supply chain by implementing clean production and appropriate waste management at their own factories, as well as those of their suppliers. Procurement bodies need to integrate environmental criteria in contacts with suppliers of antibiotics and other pharmaceuticals. Regulators must also act to include environmental criteria in the GMP framework and should be demanding more transparency in the pharmaceutical supply chain.

When it comes to addressing the global antimicrobial resistance challenge, tackling drug resistance due to irresponsible production and opaque supply chains is low-hanging fruit. This is an issue that must be addressed head-on across the board - failure to act will negatively impact the reputation of the industry as a whole.

Is the pharma industry taking appropriate action?

We believe the pharma industry as a whole has been shockingly slow to take action on pharmaceutical pollution. More progressive companies are only now beginning to act on a decade's worth of scientific evidence regarding the contribution of pharmaceutical pollution to the development of drug resistance. And at the other end of the spectrum, some players are clearly in denial. In India, civil society organizations have spent

decades denouncing the pharmaceutical industry's terrible environmental record but to no avail. Not all of these companies are household names in Europe and the US, but many of the firms they supply drugs to are. All players – whether they are simply purchasing APIs or other products from contract manufacturers, or manufacturing directly – have a duty to act on stamping out pollution in the drug supply chain.

Companies sometimes blame lax regulation for environmental violations in the supply chain. While it is true that governments and regulators must clamp down on bad practices, the bottom line is that this is a supply chain issue that companies themselves have a responsibility to address.

References

1. *Changing Markets, "Superbugs in the supply chain", (2016). Available at: http://bit.ly/2jZY0Xf. Accessed February 2, 2017.*
2. *J O'Neill, "Antimicrobials in agriculture and the environment: reducing unnecessary use and waste", (2016). Available at: http://bit.ly/2d36sEH. Accessed February 13, 2017.*

The Art of Science

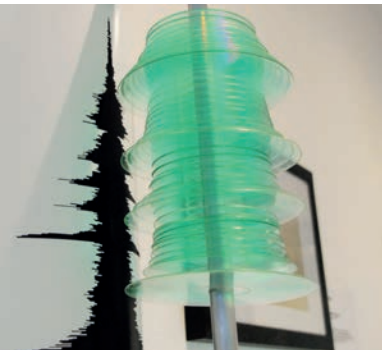
An art gallery at Pharmapack showcased the artistic side of primary drug delivery devices

We love art at The Medicine Maker and at the recent Pharmapack trade show in Paris, France, an art gallery called "The Art of Sharp" caught our attention. The gallery was developed by Terumo Pharmaceutical Solutions, a global medical technology company, and was accompanied by an audio tour.

"It was a very different approach for the company because it was a complete change of direction and it took us out of our comfort zone," Ireen Stanford, global marketing communications manager at Terumo, admits. "Our biggest challenge was aligning our internal stakeholders; we had to get them on board with our vision and give them the confidence that this was a risk worth taking."

The artwork was linked to Terumo's products and aimed to reflect the company's story, Japanese heritage, innovative work and values. "We had a very busy stand and a very positive reaction from the audience; they appreciated the entertainment and education that they got with the audio tour," says Stanford. "It was something different, which broke through the normal exhibition process and gave them a new and memorable experience. Many people returned several times!"

If your company has ever combined art and pharmaceuticals we'd love to hear from you: Stephanie.sutton@texerepublishing.com. *SS*



Photos: Copyright Terumo

The Art of Our Sister Publications

If you are familiar with our sister publications, you may be aware that they publish an annual art feature that showcases the artistic side of science.

The Analytical Scientist
https://theanalyticalscientist.com/issues/0816/analytic-x-aesthetic/

The Ophthalmologist
https://theophthalmologist.com/issues/0616/the-art-of-eyes-anterior-segment/

The Pathologist
https://thepathologist.com/issues/0816/through-the-looking-glass/

The Translational Scientist
https://thetranslationalscientist.com/issues/0716/the-art-of-translation/

Breaking with Tradition

What does the legalization of medical cannabis mean for conventional pharmaceuticals?

Do people change their use of prescription medications when cannabis becomes a legal alternative? Father–daughter research team W. David Bradford and Ashley Bradford, from the University of Georgia, trawled through the data to uncover the truth, and their findings could play a part in the rescheduling of medical cannabis – as well as speaking volumes about public opinion.

The Bradfords analyzed data on prescription drug use in the US from 2010 to 2013, focusing specifically on patients covered by Medicare Part D, the federal government program that subsidizes prescription drugs for people over 65 – an age range thought to be most opposed to using cannabis. "It was a question of robustness," says David Bradford, Adjunct Professor in the Department of Economics. "We had good data on Part D drug use, and believed that if we found an effect we could be confident that it was real. Ultimately, we were surprised at how statist ically significant and robust the results were."

The researchers estimated that implementing a medical marijuana law (MML) reduced Medicare part D spending by about 0.5 percent in nine disease categories. Bradford breaks this down: "In 2013, that represents $165 million saved for the 17 states and the District of Columbia that had medical marijuana laws in effect. If all states had had a medical marijuana law in effect that year, Medicare Part D spending would have been about $470 million lower."

The team has already examined the effect of MMLs on opiate-related deaths in the US, and found that opiate deaths fell significantly when states implemented dispensary-based MMLs. They have also examined the impact of MMLs on Medicaid prescription drug use, and the findings were even more noteworthy: "The magnitudes in Medicaid were a good bit larger – 2 to 4 percent reductions in Medicaid spending when MMLs go into effect, compared with a one-half percent reduction for Medicare."

The report certainly has garnered attention, both in scientific spheres and across the media, with references to the work made in at least one US Senate hearing. But the Bradfords were more interested in another implied aspect of the findings. "Patients and doctors together are treating medical marijuana as a real alternative to pharmaceutical medication," says Bradford. This, if true, emphasizes the importance of further scientific research – with better healthcare being the ultimate goal. *JC*

Reference

1. *AC Bradford, WD Bradford, "Medical marijuana laws reduce prescription medication use in medicare," Health Aff, 35, 1230–1236 (2016).*

This story was first published in The Cannabis Scientist, a supplement to The Analytical Scientist. https://theanalyticalscientist.com/

Pharmtastic Voyage

Scientists develop a microscopic "submarine" that neutralizes gastric acid for fuel to safely deliver drugs to the stomach

In the 1960's science fiction movie, Fantastic Voyage, Dr Jan Benes is left comatose with a life-threatening blood clot after a Soviet assassination attempt. Captain Bill Owens and his crew have only 60 minutes to board a miniaturized submarine and make their way to the clot, operate, and exit the body before they are returned to normal size, killing the unfortunate Benes.

Since its 1966 release, Fantastic Voyage has been widely celebrated, satirized, and now – with a new device developed by Jinxing Li and his team from the Department of Nanoengineering, University of California San Diego – imitated. Although there's no "atomic miniaturization" involved, Li's team have developed a microscopic "submarine" that can speed through the stomach using gastric acid for fuel (while simultaneously neutralizing

it) and release cargo precisely at the desired pH. The "submarine" is actually a proton-driven, biocompatible micromotor with a pH-dependent polymer coating that can be loaded with drugs.

"Fantastic Voyage features a microscopic submarine that travels inside the human body to treat life-threatening issues," says Li. "We're aiming to apply our micro/nanomachines to drug delivery, detoxification and precision surgery."

A number of pH-sensitive compounds are vulnerable to gastric acid – including protein-based drugs and some antibiotics. An enteric coating can usually do the job of preventing degradation in the stomach, but for drugs that need to be activated in the stomach, for instance to treat stomach ulcers, proton pump inhibitors are usually needed to block gastric acid production. When used over longer periods, these can cause some side effects, including headaches, diarrhea, fatigue and, in some severe cases, rhabdomyolysis, a potentially life-threatening muscle disease.

Li's micromotors are microscopic spheres consisting of a magnesium core, which reacts with gastric acid to generate bubbles for propulsion. This process also neutralizes the stomach pH spontaneously (1). "Such motor-induced neutralization of the stomach fluid further triggers the autonomous payload release from the pH-sensitive polymer coating," says Li.

Where proton pump inhibitors suppress acid in the stomach, the micromotors alter the local environment without blocking the function of the proton pumps. "This approach hardly interferes with the function of the stomach and therefore completely eliminates the side effects associated with proton pump inhibitors," says Li.

Li hopes that the technology will help improve treatment efficiency since the propulsion of the micromotor allows it to penetrate the gastric mucosa, which increases the amount of time that the drug is retained in the stomach.

The journey continues as Li's team turn their attention to loading real therapeutic agents to treat stomach infections. *JS*

Reference

1. *J Li et al., "Micromotors Spontaneously Neutralize Gastric Acid for pH-Responsive Payload Release", Angewandte Chemie International Edition, (2017).*

Business-in-Brief

Beating the backlog, a campaign to counter criticism, and a first foray into biosimilars… What's new for pharma in business?

Regulation

- A report by the US Government Accountability Office (GAO) has found that the FDA has a backlog of 1000 foreign sites, despite the fact that, over the past decade, the FDA has nearly tripled the number of foreign inspections it carries out per year. Over the past five years, the FDA has also reduced its catalog of drug establishments with no inspection history to 33 percent of foreign establishments, compared to 64 percent. However, according the GAO, "the number of such establishments remains large, at almost 1,000 of the approximately 3,000 foreign establishments. FDA plans to inspect all of these establishments over the next 3 years."
- Last month The UK Prime Minister Theresa May signaled that she intends to take the UK out of the EU single market and customs union with potential significant implications for trade and investment. But what about the EMA? Health Secretary Jeremey Hunt said that he "doesn't expect [the UK] to remain within the EMA." He went on to say "we could potentially have mutual recognition" and he will be arguing for the "closest possible relationship."

Politics

- Should the US government buy Gilead? Writing in Forbes, Peter Bach and Mark Trusheim argue it would cost the taxpayer around $156 billion upfront, but by divesting unneeded assets and repatriating Gilead's overseas cash (tax-free of course), the final price would come to $40 billion – or $15,700 per patient. That's a 63 percent saving on the $113 billion ($42,000 per patient) it would cost to treat all those still infected with Hepatitis C. "Ideology matter less when the numbers work," say the authors. "In this unique case they do."
- PhRMA has unveiled a new campaign to counter industry criticism. The first television ad, which features Dylan Thomas' poem "Do not go gentle into that good night," juxtaposes pills and photographs of presumed patients, and shows fastidious scientists pacing down hallways and peering through microscopes. The PR campaign aims to "explore the innovative research and technological breakthroughs of America's biopharmaceutical industry and get to know the people behind the fight to prevent, treat, and cure disease."
- Marathon Pharmaceuticals has paused the US commercial launch of its newly approved treatment for Duchenne muscular dystrophy, Emflaza (deflazacort), after a backlash regarding the price tag of $89,000 per patient per year. US patients have been importing generic versions of the drug from Canada and European countries for years and using it off-label, at a much lower cost. Critics have pointed out that Emflaza is not a revolutionary treatment and have also accused the company of abusing the FDA's orphan drug program. Marathon have attempted to explain the need for a high price in an open letter to the Duchenne community.

Manufacturing

- Eli Lilly has halted its planned €200 million expansion in Cork, Ireland, reportedly over concerns around Donald Trump's latest plans. A spokesperson for the multinational told the Irish Examiner that a final decision on whether it will proceed is now under review, and will be made by Lilly's global board at the "appropriate stage of the process," reports Newstalk.
- India's Aurobindo Pharma has moved into biosimilars development with the acquisition of four products from Swiss company TL Biopharmaceutical AG. As part of this agreement, TL will supply all the developmental data for four molecules and Aurobindo and/or its affiliates will develop, commercialize and market the products globally.

For links to the original press releases, visit the online version of this article at: http://tmm.txp.to/0217/business

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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

Pharma to the Rescue

We need to engage with patients more. What better way than partnering with Marvel Custom Solutions to create a graphic novel that depicts patients as "Super Heroes"?

By Danny Stepto, Global Product & Pipeline Communications at Takeda Pharmaceuticals.

Last year, I had the opportunity to attend Comic Con in London, UK. I was there with my Takeda colleagues to raise awareness of inflammatory bowel disease (IBD) in a pretty unusual way. With the support of Marvel Custom Solutions, Takeda unveiled a group of "Super Hero" characters and the first chapter of a new graphic comic book. This global initiative – IBD Unmasked – has been designed to highlight both the daily battles and the remarkable strength of the unsung heroes of the global IBD community. I'm proud to say that Takeda is the first pharmaceutical company to partner with Marvel Custom Solutions on a disease awareness campaign.

The team, called The Unbeatables (comprising Samarium, Switchback, Rubblerouser, Datawave and Luminaria), was created with input from a panel of IBD patients from around the world. The members of The Unbeatables are connected to IBD in some way. For example, the character Samarium has ulcerative colitis and Luminaria is a nurse in frequent contact with people who have IBD. I was touched by how the initiative resonated with people at the event in London. The pharma industry has an ethical responsibility to support patients throughout their entire journey, which includes helping them to understand their diseases better. It's not just about making medicines.

Disease-awareness campaigns are, of course, a common way to disseminate information, but it can be difficult to cut through the noise and to truly strike a chord with patients of all ages. We wanted to do something that focused on IBD because this is something that Takeda knows a lot about. It's a chronic disease that patients have to live with throughout their lives – many patients can begin to see symptoms in their teens or early twenties, which may include stomach pain, recurring diarrhea, fatigue and weight loss. IBD can be a very isolating disease because patients often feel very embarrassed to talk about it – something that is true for many diseases. I believe it is an area where pharma companies should be stepping up to help. Yes, typical resources that companies put together have a place, but surely we can be more creative in our approach.

Heroes cut across cultures and age groups and the idea of fighting villains is quite an apt analogy for patients who are battling with symptoms every day and often wear "masks" to hide their condition from others. And who was better to partner with for the initiative than Marvel, as well as people who spend their life fighting their IBD?

Everyone involved in the project is incredibly invested – from the patient panel to the artists. The Marvel illustrator of the graphic novel cover, who lives with IBD herself, actually found out about the project through her local patient advocacy group and put herself forward to help because she was so eager to get involved.

Pharma is heavily regulated so it can be difficult to be innovative at times, even

with a disease-awareness campaign. It's important not to trivialize a disease, or to appear patronizing, and if you're using a story-telling approach then the voices need to be authentic. IBD Unmasked is a global campaign that will be rolled out around the world in the coming year. The graphic novel will also be available in a variety of languages. The first chapter launched in 2016 and we hope to launch the second chapter in the coming months. Over time, we'll create the complete graphic novel, with each, chapter revealing more about each of The Unbeatables. We're not just exploring how individuals manage their symptoms, but how it affects their relationships with family, friends and healthcare providers.

From the start, I firmly believed the project would bring value to the community and it was an eye-opener to be at Comic Con (in more ways than one); many people came to our booth to tell us that they had IBD and were genuinely pleased by the characters we had created. These people certainly didn't go to Comic Con intending to talk about IBD so I think it's great that we could start to encourage people to open up. Graphic novels won't resonate with everyone, but they do seem to be a good medium for young adults – a group of patients that is vastly under-served.

I encourage other companies to think more creatively about how they might approach a disease-awareness campaign that can really resonate with patients. The rewards for doing so are very humbling. One recent compelling moment for me was when a patient sent us drawings of herself as a superhero. Isn't it great to make patients think like that?

Why Encapsulation Is (or Should Be) King

Every dosage form has its advantages – and we all have our preferences, either as formulators, manufacturers or consumers. But for modern medicines, I believe that liquid-filled encapsulation has the edge.

By Stephen Brown, Managing Director at Capsugel, Edinburgh, UK.

It has been said many times that the shape of capsules makes them easier to swallow than tablets – and there are others in the industry that maintain the opposite. I've not hidden my affiliation above, so you can probably guess where my allegiance lies! Oral dosage forms come in all shapes and sizes. Whether a capsule, liquid, powder, pellet or tablet – each has a role in drug delivery. But what if we could combine two forms into one? Instead of re-treading the old ground of which dosage from is better, I'd like to focus on discussing why encapsulation is perhaps more future proof than tablets. One of the key benefits of capsules is the ability for liquid fill – and this technology lends itself to some important trends in APIs.

Firstly, although solid dosage forms are generally well received by patients, many new chemical entities are relatively insoluble in aqueous media, resulting in slow and incomplete dissolution in the intestinal milieu. Liquid formulations of drugs – either in solution or suspension – help address solubility issues, but are not always convenient to take. Liquid-filled capsules, in my view, offer the best of both worlds. And the very reason I started working with liquid-filled capsules was because I firmly believe that the advantages of the technology hadn't been fully exploited. A liquid formulation designed for encapsulation retains the convenience and simplicity of oral solid dosage form delivery. Many compounds in the pipeline today exhibit poor solubility and require bioavailability-enhancing technology. In many cases, lipid-based formulations can significantly improve the solubility of an API – and dispersions or suspensions of drugs in lipidic vehicles or solvent and co-solvent approaches can be readily encapsulated into either capsules or soft gels.

Secondly, I believe that liquid formulations are also well suited to meet the formulation and safe handling challenges of high-potency APIs (HPAPIs), which make up an increasing proportion of industry pipelines. High potency drugs enable therapeutic efficacy at low concentrations. But while that may be clinically advantageous, they also complicate drug development and manufacturing processes. The required dose of a HPAPI is very low – sometimes less than a milligram – and it can be a challenge to achieve dose homogeneity. Ensuring uniform HPAPI content in each tablet, for example, requires careful selection of appropriate excipients, rigorous mixing studies at each scale of manufacture, and monitoring for powder de-segregation, which could translate to significant dose-to-dose variability. In some cases, companies have had to cease manufacturing particular products because they just couldn't achieve dose reproducibility. Protecting operator safety is another key issue at all stages of

product development and in my view, liquid fill technology minimizes the potential for operator exposure compared with the handling of solid active ingredients.

An example of a low-dose product with potency and bioequivalence issues that liquid formulation helped to address is levothyroxine. Levothyroxine was the subject of a review by the UK's MHRA in 2013, which concluded that levothyroxine tablets were difficult to manufacture. As a result of the potential sensitivity of levothyroxine products to minor changes in processing technology, the manufacture of levothyroxine products should be considered "non-standard" despite using conventional blending, granulation and compression technology. And here is where a liquid filled capsule has a chance to shine. Liquid-filled capsules can accommodate low doses with good dose-to-dose reproducibility, as the drug, once in solution (or well-formulated suspension), is homogeneous, with no opportunity for de-segregation during capsule filling or product storage. The levothyroxine example offers an excellent case study in which liquid-filled hard capsule technology was shown to be capable of generating formulations of this drug with good dose reproducibility, hence avoiding the pitfalls associated with levothyroxine tablets.

I am sure it's clear that I'm passionate about the potential of liquid-filled hard capsule technologies, but they are just one of many dosage forms that can help deliver ingredients to the body in the best way. In fact, there are some instances where tablets, pellets, liquids or powders may trump a capsule. Drug development, however, is becoming more complex and I think it is well worth the industry looking to advanced technologies. In particular, it's important to choose the solution that best suits the characteristics of the API, meets the target product profile, helps ensure operator safety, and ultimately provides the best therapeutic outcome for patients.

The Human Challenge

We need to get better at predicting the real-world efficacy of vaccines. Human challenge studies are one possible way of achieving this.

By Adrian Wildfire, Project Director for Infectious Diseases & Viral Challenge Unit at SGS, Belgium.

Vaccines have played a huge role in improving human health, but there is still a great need for new and improved vaccines. Despite decades of innovation, vaccine development remains challenging. Immunological responses are frequently difficult to measure and the mechanisms underlying how an immunological response confers protection remain poorly understood.

Traditionally, vaccines are tested in late-stage trials against naturally circulating viruses in the community. Many thousands of people are inoculated with the developmental vaccine in the hope that a sufficient number will encounter the virus for its protective index to be calculated. This approach can be hit and miss. For example, if the incidence of infection at the time is low, there may be insufficient responses to provide statistically significant results. Other circulating viruses can also interfere with the observation of symptoms, making for "noisy" data. In addition, trials of this type are expensive – and often fail when early evaluations of efficacy or safety in small numbers of healthy volunteers don't translate into larger, more heterogeneous populations. Indeed, a key question for vaccine development is, how can predictions of a vaccine's real-world effectiveness be improved?

In my view, it's time for more developers to consider the human challenge model. Human challenge trials involve deliberately infecting healthy volunteers with a target organism, such as influenza, in order to test the effectiveness of a vaccine at preventing illness. By challenging people with a live, disease-causing pathogen post-vaccination, it is possible to assess responses in vivo, and to compare the course of disease to that in unvaccinated subjects. Does it give a muted infection, or completely block the entry of the pathogen? Does it reduce the symptoms, or shorten the duration of the illness?

Regulatory authorities have (understandably) been wary of embracing the concept of a human challenge trial – after all, it uses live infectious agents and makes people ill. There are, of course, a number of considerations, including ethics, but more human challenge trials are gaining approval – and both the EMA and FDA say they are open to discussions with companies wishing to conduct such trials. Important prerequisites for approval are units with effective containment and a challenge agent that is an effective surrogate for the wild type infection – but usually with a milder pathogenicity.

The study is performed in small groups of healthy volunteers. Firstly, the subjects are tested to ensure they are not suffering from any other infection and to check their immunity status regarding the challenge agent (they must be susceptible to infection). If the study is for a vaccine,

vaccinations will be administered three or four weeks ahead of the trial. The challenge virus is usually administered via an intranasal spray. With an influenza infection, the virus will start replicating rapidly after 12 hours. Symptoms tend to lag behind viral load and are usually reached in 72 hours. During the period of infection, many signs and symptoms will be monitored, such as body temperature, pulse rate, lung function and the amount of mucus produced, as well as viral shedding and antibody levels. Subjects also fill out a symptom scorecard. All of this serves to give a good indication of how effective the vaccine was at preventing disease – and the early efficacy and safety data is immensely valuable to vaccine developers.

There are, of course, still challenges associated with human challenge trials. The biggest is finding the right volunteers. Any center equipped to run a human challenge study will have a database of potential volunteers, but the size of the volunteer pool will depend on the infection rate in the population. For example, about 95 percent of potential volunteers have already developed immunity to the 2009 pandemic H1N1 strain, so cannot be included in trials using H1N1 as a challenge agent. In contrast, a much smaller percentage of the population (usually around 25-50 percent) will have immunity to a recently developed challenge virus that has not circulated for long in the general population.

It should be noted, of course, that not all diseases are suitable for human challenge studies. At this moment, challenge trials are largely limited to upper respiratory tract infections – notably RSV, influenza and the common cold. We desperately need new innovations in vaccines and human challenge trials offer many benefits in terms of delivering efficacy and safety data. They also tend to be faster and cheaper than community-run trials, which may require hundreds or even thousands of subjects, recruited across several flu seasons, and in both northern and southern hemispheres. A challenge trial can be completed in around three months.

In my view, challenge trials will become more commonplace and rolled out in other disease areas. We are already seeing human challenge trials being used for other attenuated organisms, such as dengue and malaria, and discussions are taking place about human challenge trials for Zika. In the future, we may even envisage the use of replicatory deficient agents being used to model chronic infections, such as HIV or hepatitis.

An Intense Focus on Perfusion

Continuous manufacturing technologies are seeing increased industry uptake, particularly perfusion systems and, increasingly, intensified perfusion. Perfusion offers many benefits to bioprocessing, but choosing the right system and the right medium are key.

Perfusion systems differ from their fed-batch counterparts in that they permit bioreactors to run continuously over extended periods of time by constantly perfusing fresh medium through the culture, simultaneously providing fresh nutrients for the cells and removing waste products. The key advantages of perfusion technology include higher yields per volume, increased flexibility, more consistent product quality and lower capital investment. Furthermore, perfusion systems can be tweaked to support very high cell densities – this "intensified perfusion" can provide even higher product yields. Here, Delia Lyons, Senior Scientist, at MilliporeSigma, describes the benefits of perfusion in modern bioprocessing.

What drew you to this work?

I became interested in cell culture media about 14 years ago, after obtaining a microbiology degree and completing a two-year chemical engineering internship at Massachusetts Institute of Technology. I decided quite early in my career that I wanted to apply my knowledge in cell culture media development and perfusion technology. Today, I lead the Perfusion Media Development Team in the US for MilliporeSigma. We develop both catalogue and customized perfusion media to fit the needs of specific customers.On the one hand we make excellent media for general use, and on the other we fine-tune the media so that our clients can maximize their productivity from a given system.

What big trends are you seeing in bioprocessing?

The growing ability to target disease at the molecular level has resulted in a greater variety of new drugs – many of which address unmet needs. At the same time, processing technologies have evolved to make biomanufacturing more efficient and cost-effective. In particular, I believe that the implementation of single-use systems has been a game-changer – they are fast to deploy and negate the need for expensive and time-consuming cleaning. In terms of business trends, the industry seems to be more competitive than ever before, with many drug companies vying for market share. Patent expiries have depressed prices and there is a growing emphasis on fast-to-market development strategies. In this environment, flexible, cost-effective processes, like perfusion culture, are very attractive to manufacturers.

What is driving the industry's growing interest in continuous manufacturing?

Fundamental economics is the most important driver – the adoption of continuous processing results in demonstrable savings. Perfusion is one of the leading continuous technologies in terms of adoption in biotechnology. N-1 perfusion saves time and allows you to reduce bioreactor size in the seed train, while production perfusion processing gives much higher protein yields than fed-batch. One of the key advantages with perfusion is its flexibility – the technology is compatible with small, portable plants, and can be used with many drug types over a range of production scales. Also, often perfusion is used with hybrid systems; for example, the combination of fed-batch and perfusion processing.

Perfusion systems can be applied in different ways depending on your objective. For instance, to harvest cells, you may employ a perfusion process in an N-1 bioreactor, or to achieve high-density cryopreservation. Alternatively, if the intent is to harvest protein, you might use a production bioreactor. Generally, production perfusion is interpreted as a process in which the cells are maintained in a steady state, most commonly by active cell bleeding. However, an alternative modality quite commonly used implements a dynamic perfusion in which the cell density is not controlled and viability is allowed to drop similarly to a fed-batch process. Modalities used in the industry for perfusion protein production include microfiltration (or equivalent perfusion systems in which protein is being collected in the harvest), ultrafiltration or hybrid perfusion/fed-batch processes. That said, not all production processes are compatible with perfusion systems at present, so most probably there will always be a need for fed-batch processes. Many companies recognize this by building capacity in both perfusion and fed-batch.

What have been the main technological advances in perfusion systems?

The development of a fully closed upstream system and of more sophisticated on-line and in-line analytical capabilities has made a huge

difference to the industry by reducing the risk of losing a perfusion run, which can be costly. In my view, however, the biggest advance has been the introduction of cell separation devices that enable intensified perfusion by sustaining very high cell densities in the bioreactor. That said, there is definitely room for improvement. All current cell retention devices have some drawbacks, even hollow fiber filtration devices (currently the best at providing very high cell densities); for example, some proteins are partially retained by the filter, resulting in lower yields and reduced efficiency. There is a lot of industry interest in developing improved retention devices.

How do perfusion systems help improve product quality?

Perfusion technology allows operators to keep cells in a steady state, providing a uniform and sustained protein quality profile. This, together with the lower protein retention times in the bioreactor, result in better control of potency and immunogenicity. To get the best out of perfusion technology, however, it is very important to choose the right media. Intensified processes give cultures of at least 50 million viable cells per ml, but the cost of medium often prohibits high perfusion rates. If the rate at which we can perfuse the medium is limited, then we should focus on controlling the metabolic profile of the cells, both to minimize toxic by-products and to ensure nutrient levels are adequate for high-cell densities. Such metabolic control can be achieved by fine-tuning the medium according to the cell type and product quality requirements. To increase cell biomass – for example, for cryopreservation, or to inoculate another reactor – extremely high growth and viability rates are required. Conversely, in a production reactor, high growth rates may be unwelcome because keeping cells in steady state would require more medium to be bled off, which again impacts cost of goods. Growth rates can be controlled by careful choice and design of culture medium.

Optimizing media according to the metabolic needs of each specific clone and product and requires significant expertise. In my team, we use a combination of statistical tools and metabolic analysis, as well as the nutritional know-how we have developed over many years. We apply these resources to understand the cells and to then guide them towards customer needs. We have also developed a catalogue CHO cell perfusion medium, which is applicable to a broad range of CHO lines, but can be optimized as necessary.

What are the challenges of implementing perfusion?

Despite the economic advantages of perfusion, some companies are reluctant to make the transition. Among other reasons, a certain level of expertise is needed to run perfusion systems, perfusion has a higher risk of failure than fed-batch due to more on-line steps, and there is still some fear on being able to demonstrate process control to regulatory agencies. That said, better monitoring and sterility processes have certainly helped make perfusion systems more reliable – and I believe that the benefits are unarguable. However, in a continuous process where cell culture medium is a major cost driver, minimization of perfusion rate is critical, which means the choice of medium is the key to success. Optimized medium will significantly reduce cost of goods; for example our catalogue medium can give more than a five-fold increase in volumetric productivity as compared with fed-batch (Figure 1).

Intensified perfusion is now a reality in bioprocessing; it's just a matter of time until we see widespread uptake.

For more information about perfusion, please contact delia.lyons@sial.com

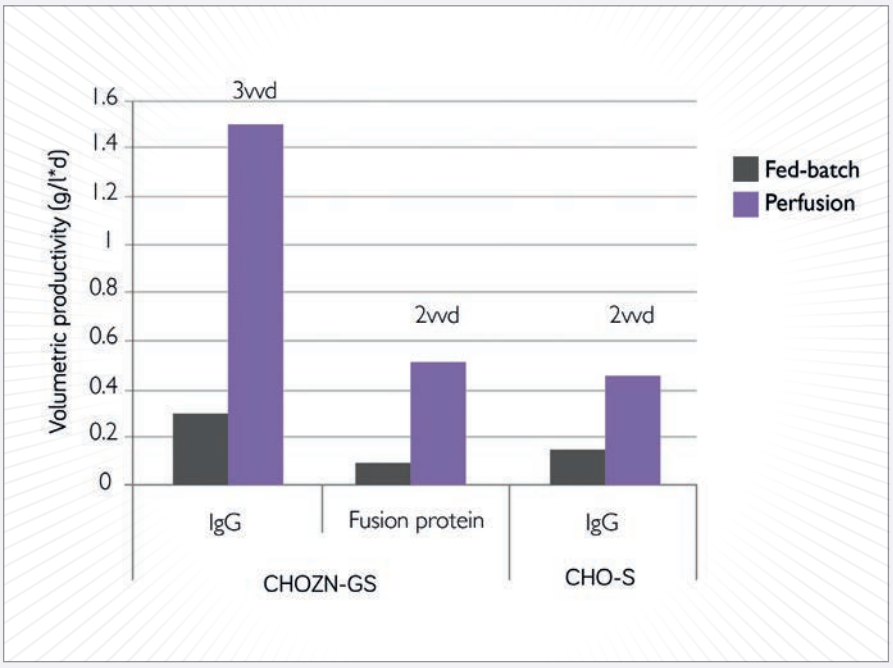
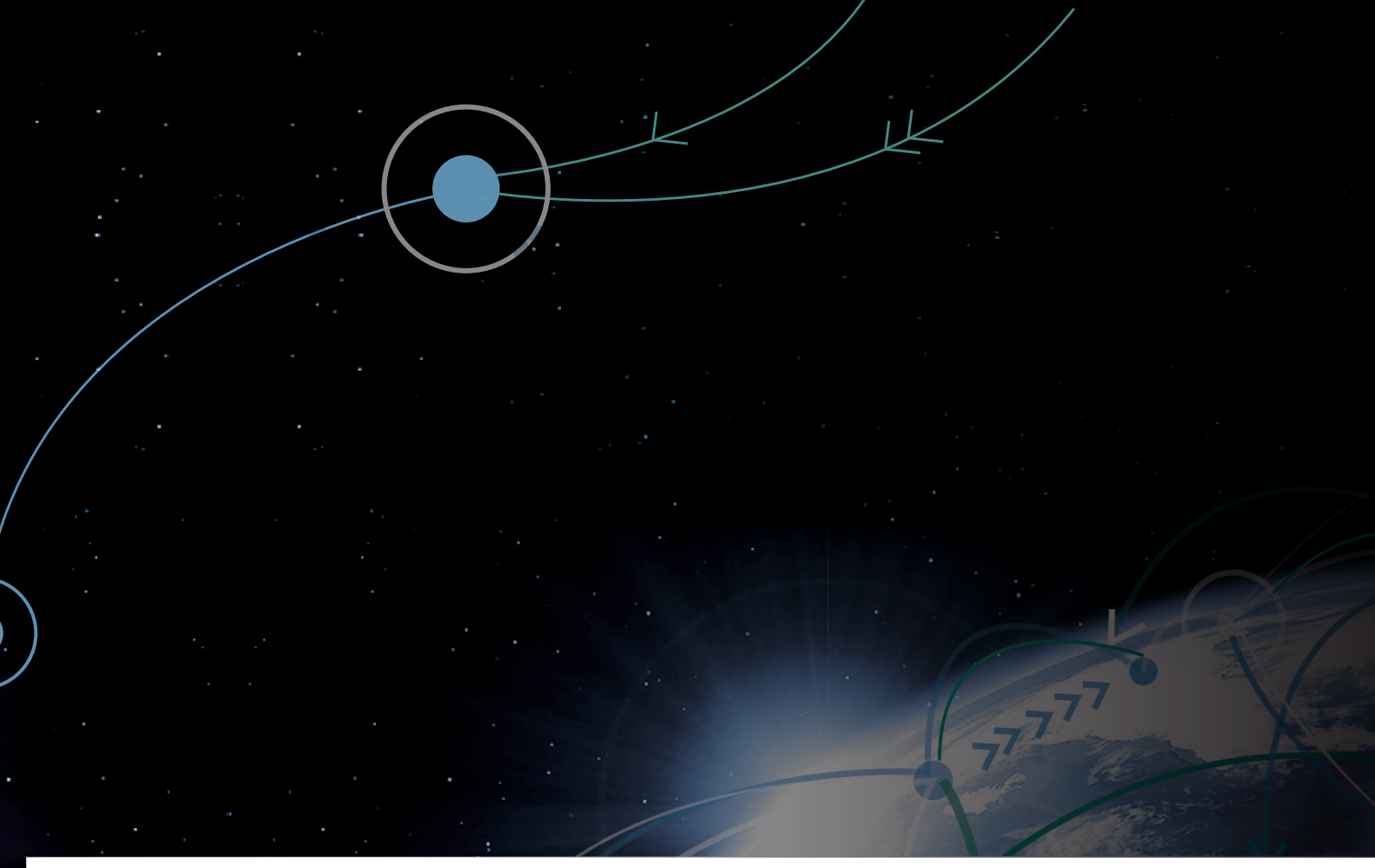


Figure 1. Volumetric production with three cell lines in benchmark fed-batch system compared to perfusion.

GLOBAL VIGILANCE

"Rx-360 was created as part of an emotional reaction to the home truth that criminals were violating our industry. My wish was to use the upwelling of strong sentiment to drive positive change."

By Martin Van Trieste



To tell the story of how Rx-360 began, I first need to set the context...

In the mid-2000s, the pharma industry really started to embrace globalization – after all, it allowed the industry to increase its customer base dramatically. The economics of globalization, such as the cost of goods supplied and tax implications, were certainly intriguing from a business point of view. But there were also bumps in the road in terms of the robustness and reliability of the supply chain; for example, the quality of materials being sourced from different countries. At first though, there was nothing too alarming and the general industry consensus was: "This is an immature market but we'll develop it and make it a success. Every road has its bumps, but our industry is full of smart people so we can fix it."

And then the heparin tragedy struck. In 2007 and 2008, some patients being treated with heparin became very sick and a number of patients died. As the situation unfolded, the US Centers for Disease Control and the FDA started to investigate, and found that the problem stemmed from raw heparin stock manufactured by Scientific Protein Laboratories in China and imported into the US by Baxter.

Heparin is a naturally occurring by-product of pork and it generally takes one slaughtered hog to produce one human dose of heparin. The world's largest consumer of pork is China, which unsurprisingly also happens to be the largest breeder and slaughterer of hogs. Prior to the heparin tragedy, there was a viral outbreak in China that devastated the hog population, creating a shortage of pork and pork by-products. Prices started to soar, and in some cases the price for heparin increased three-fold during this period. Despite this, deliveries of heparin API remained consistent and reliable – something that should be impossible during a shortage. And yet we, as an industry, failed to recognize the warning sign.

Eventually, it was discovered that the workshops producing crude heparin intermediate were substituting it with over-sulfated chondroitin sulfate. Over-sulfated chondroitin sulfate looks like heparin, passes heparin assays of potency and purity, and even imparts a similar human therapeutic effect to heparin as it thins blood. The substitution allowed the workshops to meet their demands, win higher prices and use less expensive raw materials. They were only caught when patients started experiencing adverse reactions. The number of deaths attributed to the tragedy vary depending on the literature, but the FDA has said that at least 81 deaths and around 785 injuries were linked to heparin. If we just consider numbers, we may not be moved, but families were devastated by the incident. There is a powerful video available online showing the families of victims testifying in front of US Congress about the impact of adulterated heparin. One gentleman lost his wife but, at the time, the cause of death was unknown. Thirty days later, he lost his son, who was also taking heparin.

LEARNING FROM (BIG) MISTAKES

Even before the heparin tragedy unfolded, I was becoming increasingly concerned for the safety of our industry's supply chains. Globalization certainly has benefits, but there are also downsides. Earlier in my career, when the companies that I worked for started to buy raw materials from countries with less developed regulatory systems and oversight, I saw far too many supply and quality problems stemming from unethical behaviors and even criminal activity – the likes of which I had never seen before. As a result, I had to establish policies and procedures at those companies to prevent the purchase of raw materials from these types of countries – and I had to defend my policy, which meant I needed data. I spent countless hours researching the issue, and found that quality and supply problems were hurting not only pharmaceuticals, but also other global industries.

In the aftermath of the heparin tragedy, the PDA and FDA co-sponsored a workshop on supply chain security. The FDA's Janet Woodcock explained how pharmaceutical companies and the industry had failed to protect patients – and issued a call to action to address the problem. At the conclusion to that conference, Dr Luann Pendy (who was VP of quality at Hospira at the time) spoke emotionally about how embarrassed she was for our industry and how she was determined that a repeat of the heparin event would never happen on her watch at her company. I was also at the meeting. I was overwhelmed by the emotion in the room. People from industry cried when hearing stories from patients, while others banged their fists angrily on their table, demanding action.

The heparin adulteration was intentional and it was criminal. I realized that the GMPs we all use and rely upon every day are like the lock on the front door of my house – they are only good enough to keep the neighbors' kids out, and will never keep criminals from entering and stealing what they want. GMPs are designed to keep honest people honest, not to stop criminal behavior. I realized that the systems my company had in place were not sufficient. But I also realized that, while working for a biotech company, there was no way that I could ever put processes and systems in place that were broad and sophisticated enough to stop international criminal organizations.

As I reflected on the workshop and the emotions, I felt the time was right for the pharma industry, its suppliers, policymakers, regulators, non-government organizations, and other trade and professional organizations to work together to address the issues of counterfeit, adulterated and substandard materials in the globalized supply chain. It goes back to the saying, "never let a crisis go to waste." We had a platform to get people to do things that they had never done before, in a common interest to serve patients. It was around this time that I came up with one of the taglines that I use in almost every presentation that I make today: "Serving patients is a privilege, and that privilege comes with significant responsibilities; these include, but are not limited to, delivering quality medicines in a robust and reliable supply chain." After the workshop, I sat down with a few of my peers – heads of quality from other companies – to discuss what we had heard over drinks in a bar. And we agreed to work together. I prepared a business plan to start Rx-360 and, on Christmas Eve in 2008, I had a teleconference with the same individuals, together with others who joined in, to discuss the plan. Rx-360 was born and the founding members were Abbot (now Abbvie), Amgen, AstraZennca, GlaxoSmithKline, and Pfizer within the first 6 months, followed by Alcon, Baxter, Bristol-Myers Squibb, Cephalon, Hovione, Merck, Schering Plough, and Watson.

RX-360 RISES

Everything moved very quickly from there. We developed Bylaws, a Charter, and a website (I was the webmaster; I never thought that a 50-year man like me could become a webmaster!). The aim of Rx-360 was to help share information and to develop processes to improve the security of the supply chain – and the quality of materials within it. In June 2009, we held a launch meeting in Washington DC where we also incorporated Rx-360 as a non-profit pharmaceutical consortium. I invited around 50 people to attend and arranged for a conference room in Washington DC that would hold about 50 people. But I received more interest than I anticipated, and had to cater for 75 people, then 100 people, and then 150. We ended up with over 200 people squeezed into a room meant for 175 (they didn't have a bigger room) – and we had to turn others away. I think it's testament to how much

"SERVING PATIENTS IS A PRIVILEGE, AND THAT PRIVILEGE COMES WITH SIGNIFICANT RESPONSIBILITIES."

emotion and passion there was around the topic.

One of the core elements of Rx-360 is a joint audit program, which allows consortium members to cosponsor audits. This isn't new – it happens in many other industries, so after the Christmas Eve meeting I approached various organizations, including the International Air Transport Association (aviation), AIB International (food standards) and CHWMEG (environmental health and safety), to help figure out how Rx-360 should work. They were happy to share what they had learned and where they had made mistakes, so setting up the processes for the shared audits was fairly straightforward.

The bigger challenge was actually getting companies to actively participate. People were certainly interested in what we were doing and passionate about patient safety, but pharma isn't used to collaborating in the kind of way we were asking them too – by sharing information and audits. Most pharma companies believe that everything they do is somehow proprietary and gives them a competitive advantage. It is a perception that is irrational, especially given the number of people that move between different pharma companies; people always bring best practices from their old company and compare them with the new company. Moreover, in what way is an audit method proprietary? It's not. How you develop a molecule, the attributes of that molecule, and how it treats disease are the competitive advantages. Audits are about ensuring patient safety – and patient safety should never be a competitive advantage.

I spent a lot of time meeting with pharma companies and persuading them to join. (I should add that one of my personality traits is that I am the most persistent person you will ever meet; I am not afraid of rejection and if I believe in something then I will continue to go back and bug people over and over until they submit to the merits of my argument). There was one story I liked to tell in particular. When I was a kid, Volvo used to run a commercial that said that Volvo invented the seatbelt and had many patents on the seatbelt but, because seatbelts were such a life-saving device, they felt it was inappropriate for other cars not to have a seatbelt – so Volvo gave away their patents for free. In the pharma industry, how we perform audits and protect the supply chain is like a seatbelt – and the logic resonated with many people.

That said, there were valid concerns from a legal perspective. If I give my audit to Pfizer and Pfizer used it, but then something bad happened as a result of something I didn't find, am I liable? Tricky ground. But I was reassured by the fact that CHWMEG does shared audits in the area of health and safety – they originally did audits for the oil and gas industry before broadening their reach. Ironically, many pharma companies told us their legal team was not comfortable with the idea of shared audits, even though it turned out the company was already using the CHWMEG shared audit process to do environmental, health and safety audits of their suppliers! In the end, we were able to get people talking

"I REALIZED THAT THE GMPS WE ALL USE AND RELY UPON EVERY DAY ARE LIKE THE LOCK ON THE FRONT DOOR OF MY HOUSE – THEY ARE ONLY GOOD ENOUGH TO KEEP THE NEIGHBORS' KIDS OUT."

to break down some of those barriers.

Another legal concern was antitrust issues and anti-competitive issues. What would the US government say if we were working together collaboratively in this space? Would they say we are hurting one supplier in favor of another? That we are putting too much pressure on the supplier so they feel they have to lower the price? These concerns had a lot of merit so we filed a petition with the US government, presenting our business model and why it was in the best interests of patient safety. We obtained a Safe Harbor, which allows us to operate without fear of prosecution or antitrust issues from the US government.

Overcoming all of these challenges took a tremendous amount of time. I was fortunate that I was respected in the industry – and that I had the support of my company, Amgen, at the time. I remember speaking with the CEO of Amgen – Kevin Sharer – about the heparin incident and he asked me if the same thing could happen to Amgen. I told him straight: "Yes, it could." I also showed him the Rx-360 business plan and, because he understood the implications for both Amgen and, more importantly, patients, he gave me the freedom to use company resources, including project and program managers, attorneys, communications people and my staff. I have to give a lot of credit to Kevin for all of his support.

SECURING SUPPLY CHAINS

Things have a come a long way since the Christmas Eve teleconference. Today, Rx-360 has more than 100 members, including pharma companies, regulators, non-government organizations and charitable organizations who provide medicines to third-world countries. I am so proud of its accomplishments.

Rx-360 was actually the first organization to report a real example of so-called "shadow and show" factories in China, leading to several members finding such factories through supplier audits and reporting them to regulators. For those unfamiliar with this term, it involves a showcase factory that meets all the necessary regulations, but in reality the work is often pushed out to other "shadow" factories that may not have the same standards.

At any given time, there are over 500 volunteers working on various Rx-360 activities, which includes issuing "flash reports." For example, if there is a new guidance document being issued we will review and summarize it. Our flash reports are free to anybody who wants to see them – they are a fast, effective way of disseminating information to the community. We also occasionally issue "Rx-360 Alerts" where we share a real defined risk to the pharmaceutical supply chain. For example, if we find out about a potential raw materials shortage, we send notices out quickly and develop a list of things our members should do to protect themselves, such as including special test methods to ensure a product has not been adulterated.

We also issue best practice and guidance documents (available on our website for free). In 2011, for example, we developed guidance on how to deal with the events surrounding the huge earthquake that hit Japan and the resulting nuclear accident. We developed a team of people consisting of nuclear experts, safety experts, medical doctors, quality and manufacturing people, and supply chain experts from around the globe to examine two

critical areas. i) How do we know the raw materials produced and stored in Japan around the impacted zone are safe for us to continue to use? ii) How do we assure the population of Japan that the medicines we send in to treat them are safe and effective during the crisis? We worked closely with the FDA and guidance was issued within a few weeks.

The FDA has approached us a few times to ask us to examine certain incidents in times of crisis. For example, they approached us after the Chinese melamine disaster – where various protein-based products were adulterated with melamine, which has a similar nitrogen content, which is the basis of many tests. Infant formula was badly affected by the scandal in China – and many infants died as a result. After being asked to help, Rx-360 developed a test method that specifically looked for melamine adulteration. We provided it not just to our members, but to anyone who wanted to use it, for free.

We were also asked to help on the issue of cargo theft, which was at boiling point for pharmaceuticals in 2009 and 2010 (and is still a significant issue today). The FDA came to Rx-360 and we developed a white paper/guidance document on how to prevent cargo theft and warehouse theft. We also created risk assessment documents for companies to determine which of their products were at risk. A number of other organizations also made efforts to reduce pharma cargo theft and the collaborative efforts reduced cargo theft by 90 percent compared with before the guidance was issued.

But even as we continue to improve our industry's defenses, criminals and unethical players will constantly be trying to think of workarounds. In particular, we need to beware of complacency. Our industry has had many recent supply chain successes and is now much better at screening and selecting suppliers. By sharing information, we have thwarted many criminal and unethical acts and implemented new defenses, but we must continue to be vigilant. Unfortunately, there are many companies – both large and small – who aren't in this business for patients, but for money. And I don't believe they have robust supply chains, because it's an added cost. We should never stop talking about responsibility or about what should be driving us forward – patients.

Martin Van Trieste is recently retired Chief Quality Officer, Amgen, and Chair of the Board of Directors, Parenteral Drug Association.

MEETING MARK PAXTON

"I was so tickled when we hired Mark; he is a blessing for Rx-360 and he is a full-time leader. It's no longer myself or Brian Johnson or Lynn Byers running Rx-360 as a side job – Mark is only dedicated to Rx-360. He has a wealth of experience from the FDA and the pharma industry, and brings the unique skillset of a lawyer. He's done some fantastic work with regulators, the World Health Organization, charities, and making in-roads into China. And I have high expectations that he will continue do great things. Mark really believes in the driving mission of Rx-360 – and you have to believe for others to follow you." – Martin van Trieste

Rx-360 was initially set up with a large law firm, Drinker Biddle and Reath LLP, serving as the administrative function for the organization. As Rx-360 started grow, it became clear that it needed to migrate to a more traditional business model, which led to the search for a CEO. Ultimately, Mark Paxton was chosen for the role in October 2015.

You started out as a lawyer….

Right. I was based in Lexington, Kentucky, and one of my clients was a small pharma manufacturer called Murty Pharmaceuticals that did a lot of work for the National Institute of Health. I ended up working for them full time. It was a small company, and its president, Ram Murty, was widely recognized as a GMP expert. I had the luxury of being able to learn the pharma business inside and out. Working in a small company environment has many advantages because you get to wear multiple hats. I was director of legal and regulatory affairs, but I had the opportunity to spend time in manufacturing suites and the QC lab. Consequently, I can read an HPLC chromatogram (not bad for a lawyer, right?), developed SOPs, and most importantly, was given the time to read virtually everything that the FDA had published as regulations or guidances covering GMPs and application approvals.

How did you become interested in the supply chain?

Somewhere along the way, PhRMA got in contact with me via a headhunter. I remember thinking at the time, "Why would you be even remotely interested in me?" It happened though, and I learned so much at PhRMA – I worked with almost every major regulatory authority in the world. And during my last year and a half there, I was tasked with examining some of the issues regarding track and trace, and serialization, and it got me looking at downstream distribution channels. I was really excited about that. It's one thing to work on the approval process and drug development, but once you get into distribution it involves a different type of complexity all the way around – products go to distributors and end up everywhere. You start thinking about the kinds of controls you can put into place once the product is introduced into national or international commerce to assure the product is not improperly diverted. This has proven to be a really difficult challenge and it's an area ripe for regulatory oversight. In the US and many other countries, there are festering opportunities for diversion to occur – and it's something we've seen far too many times already. Participating in solutions for these issues directly impact patients, which is why I am pretty passionate about supply chain security.

The issue was also squarely on the agenda of the FDA Center for Drug Evaluation and Research, where I eventually had the opportunity to work. I really enjoyed my time there and cannot emphasize enough what a wonderful place the agency is. There, I focused on a large, externally-funded program through the Asia Pacific Economics Cooperation (APEC), which is a multilateral government-to-government program that aims to promote trade. I was asked to lead something called the Road Map to Promote Global Medical Quality and Supply Chain Security. The aim was to develop a holistic view of the movement of starting materials from manufacturing through distribution – and ultimately to dispensing. We were evaluating numerous gaps in supply chains leading to patient exposure to adulterated, counterfeit and diverted drugs.

How did you hear about Rx-360?

I knew Martin Van Trieste peripherally through his links to PhRMA and I'd heard about the creation of Rx-360, but I hadn't worked directly with him until I got involved with APEC. At the FDA, I had to bring many regulatory authorities and industry constituents to the table – and Rx-360 was the primary

mechanism for access to supply chain experts from industry. The roadmap is now close to fruition and it was a wonderful way to be exposed to Rx-360.

When I found out that Rx-360 was interested in changing their business model, I threw my hat into the ring for the role of CEO. The attraction for me was the opportunity to be nimbler and to offer up best practices that would allow us to close some of the gaps I'd identified while working for the FDA. The problem with looking at something from a policy standpoint is that policymaking takes time and you don't have the wherewithal to address everything.

What was your main focus in your first year as CEO?

The year 2016 was all about getting organized and transitioning to the new structure. When it comes to running an organization, there is a lot of complexity in terms of processes and procedures. I was hired as a CEO but when I joined, we'd never had an accounting function – we'd never needed one since all the membership fees went to the former secretariat. Fortunately, I am an economist so I understand accounting principles, and the need for appropriate financial controls.

Similarly, all of our document management and online collaboration tools resided in the former secretariat's servers so we had to build the infrastructure ourselves using cloud-based systems. Most importantly, I also had to replace the very significant man-hours that the former secretariat had been putting in while supporting Rx-360. In a lot of ways it was like a start-up company. The transition seems to have gone well though. When we surveyed our members, they said that the transition was seamless.

What's on the cards for the joint audit program?

The joint audit program is a significant part of the value that Rx-360 has brought to both members and non-members. As noted by Martin, the heparin tragedy highlighted the fact that our industry does not always have full clarity about what is happening upstream at the immediate supplier level, and especially multiple tiers above them. Since heparin, Rx-360 and its members have done some phenomenal work to help change this. What Martin and the other board members have achieved in making Rx-360 an advocate for patient safety, while still having to pay attention to their individual jobs and commitments to their organizations, is nothing short of incredible.

Going back to the joint audit program, it has two primary objectives. One is to lower the unsustainable number of audit requests that are being made to any given supplier. Imagine a supplier with 150 customers receiving audit requests from each of them – it's impossible to do. Our second objective is to lower the average costs for manufacturers who are required, as part of their vendor qualification programs, to perform those audits.

I'd like readers to know that every now and then I come across somebody who was involved in the joint audit program early on – and sometimes I hear something derogatory about the process and the program, but I am very quick to realize that they are talking about the way the program operated early on. Whenever you pioneer something, you cannot possibly anticipate everything – and there is nothing shameful about learning as you go along. Today, we are much different. We have a validated database where all the audit reports, auditors' qualifications, Scope of Work statements, and confidentiality agreements for every party are uploaded and accessible whenever an audit is scheduled or performed. One of the other changes we made to the program was to enter into a sole source contract with the British Standards Institute, which has a global auditing footprint. These changes have led to a far more automated and efficient process. While we are still optimizing, the processes and procedures today are far richer and more robust than they were before.

What else are you planning for Rx-360?

Although our member companies have been very strong in spreading the word about Rx-360's activities, we need to create greater global awareness of the organization and the work that we do. To that end, our Board and I have highlighted three main focus areas for 2017 that align with our long term strategic plan: improving the speed and efficiency of the audit program; addressing the highest risk supply chain threat areas through sharing of best practices amongst industry and regulatory authorities, including development of enhanced training programs; and developing and expressing greater use of external communications platforms for both members and non-members.

I believe that we also need to develop inclusive relationships with healthcare systems and pharmacies. Collectively, we need to better understand how these organizations handle medical products and in turn, these organizations need to better understand all the quality principles that go into the manufacture and distribution of products for the benefit of patients. Several years ago, stolen insulin ended up being sold in a large, chain pharmacy. How did it end up there? We need to make sure that all stakeholders understand how drugs are supposed to be distributed, not just how they are manufactured.

Finally, Rx360 needs to build on its past success by continuing to fill the niche of being the one volunteer-led consortium that looks at product integrity across the end-to-end supply chain in order to protect patients. With more than 60 current member companies and a large number of official observers, we have more than 300 volunteers engaged across more than 20 working groups addressing issues that cut across all upstream and downstream nodes of the supply chain. For this reason, all of us truly believe that we are an industry group like no other, while setting a standard for trade associations in the 21st Century.

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Chasing Checkpoints

Therapeutic modulation of checkpoint signals is bringing new treatments to cancer patients – and the industry is scrambling to find more.

By Frédéric Triebel

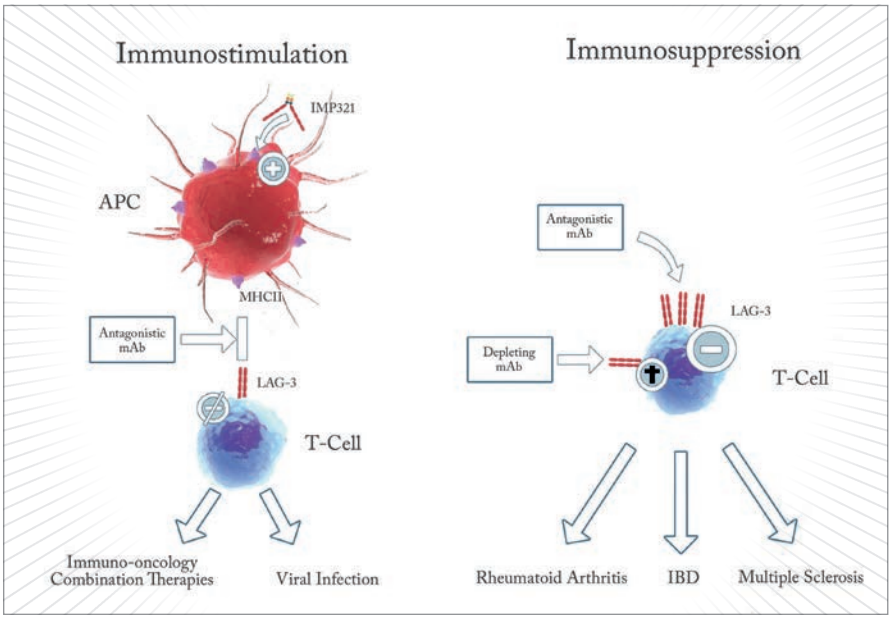


Figure 1. Targeting LAG-3 may lead to multiple therapeutics in numerous indications including immune-oncology, rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis. IMP321 is under investigation by Prima BioMed.

Checkpoint inhibitors have been identified as one of the most exciting areas of progress in the industry (1) – and with good reason. A huge amount of research from academia and industry is focusing on the potential of checkpoint inhibitors for treating cancer – and a handful of therapies have already launched. What is a checkpoint inhibitor? Many cancers produce mutant proteins that are recognizable as "foreign" by the immune system. Often, however, tumor cells also have the ability to push molecular buttons – "checkpoints" – that inhibit anti-tumor immunity. But when one door closes another opens; the elucidation of checkpoint-mediated inhibition has led to a new class of therapies called checkpoint inhibitors designed to block tumor-mediated inhibitory signals, thus allowing the immune system to mount a more effective anti-tumor response.

The potential of immunotherapy in cancer treatment has been discussed for well over one hundred years. In the 1880s, William Coley published a paper describing how he'd injected cancer patients with streptococcal cultures and observed tumour regression in some cases – but he didn't know why. What we have today that Coley didn't is a better understanding of immunotherapy, how T cells work and how cancer evades the body's natural immune system – although there is still a long way to go (2).

Inhibiting inhibition

I've spent most of my career focusing -interesting to see how the times have changed. Back when I entered the field, immunology was little more than a sub-specialty of infectious disease. During my fellowship in the 1970s, I was very focused on human tumor-infiltrating lymphocytes (TILs – implicated in killing tumor cells), which was quite unique at the time given that the vast majority of immunologists were working with mouse cells. I cloned human T cell receptors and elucidated how they could recognize two different determinants, the antigenic peptide and the major histocompatibility complex. In the 1990s, my group at Institut Gustave Roussy (France) discovered that 10-30 percent of TILs from different metastatic human tumors were of identical specificity, showing that they had recognized a tumor-specific peptide and multiplied locally (clonotypic expansion). This in turn suggested that disinhibiting this population could generate an anti-tumor response, and led to my work on checkpoint inhibitors.

Today, immunology is a vibrant area of research, and cancer immunotherapy, in particular, continues to go from strength to strength. At first, much attention focused on blocking the CTLA-4 checkpoint, which had benefits in certain groups of patients, but responses were not universal and there could be significant toxicity in some cases. So far, there has only been one FDA approval of a CTLA-4 checkpoint inhibitor: ipilimumab is a monoclonal antibody that was first approved in 2011 for treating skin melanoma – and was the first new treatment for metastatic melanoma in more than a decade. The treatment, however, can have serious side effects (3), which has spurred drug developers to look for alternative options.

Today, a lot of checkpoint inhibitor activity has focused on programmed death ligand 1 (PD-L1) and its receptor, programmed death 1 (PD-1). PD-1 is located on T cells while

PD-L1 is found on normal cells to prevent them from being attacked by T cells. PD-L1 is also found on some cancer cells. Drugs targeting PD-1/PDL-1 have been approved by the FDA in recent years – atezolizumab, nivolumab and pembrolizumab – have good response rates, but side effects can still be serious for some patients. Many more PD-1/PDL-1 drugs are being developed, but the industry is also looking to develop drugs that interfere with other checkpoints, such as lymphocyte activation gene-3 (LAG-3), killer immunoglobulin like receptor (KIR), and T-cell immunoglobulin and mucin domain-3 (TIM-3) (4). Of these, LAG-3 is receiving growing interest. A number of pharma companies are investigating LAG-3; Novartis, Merck, Regeneron, Boerhinger-Ingelheim and Bristol-Myers Squibb all have LAG-3 products in the clinic. BMS's anti-LAG-3 has been in the clinic for more than three years, and the company started five new large clinical trials last year. In fact, more than 2,000 patients are being treated with anti-LAG3.

Such progress is very rewarding to see, given that I was the one who discovered LAG-3 in the 1990s (5). I've dedicated a large part of my career to not only understanding LAG-3, but trying to make it a reality. A number of researchers have also confirmed that LAG-3 could play a role in the cancer therapies of the future (6,7). LAG-3 has a unique bi-faceted regulatory role – it participates in the negative regulation of T cells (such as cellular proliferation and activation), similarly to CTLA-4 and PD-1, but it also positively regulates antigen-presenting cells. So it could be possible to create a range of LAG-3-based products, not just in oncology but also in autoimmune disease. In oncology, LAG-3 can be used in combination with PD-1 to help with metastatic cancer – potentially providing a 50-percent

Business LAG

Academic research is pretty competitive and you have to fight for your ideas. From 1990 until 2002, my group was the only one publishing on LAG-3. At times like this, when you really believe in the potential of something, it's important to be resilient. I knew that if the immune system could recognize tumors, then it would be an important advance – potentially we could wipe out even large tumor masses. And the results I was seeing with LAG-3 were compelling.

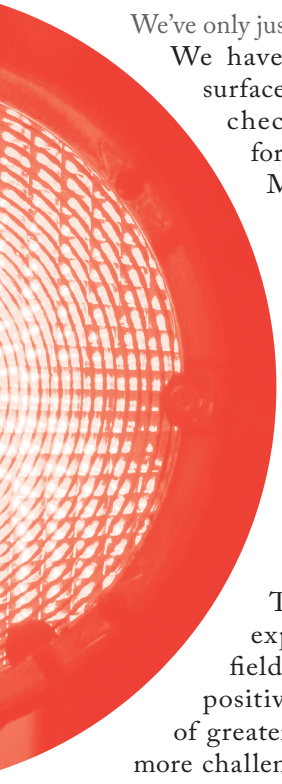
During the 1990s, I was director of a unit at INSERM – the Institut national de la santé et de la recherche médicale in Paris, France. INSERM gave the LAG-3 patents to Serono, but Sereno were not focused on moving it forward at the time. I wanted to get things moving so I quit my immuno-oncology professorship at the university with the aim of getting the patents back and starting up a new company – Immutep. Along the way, I learned just how inefficient the biotech world is. More than three years of negotiations were required to licence the patent back from Serono, and obtaining Series A funding from investors required immense effort. Series A was the last tranche raised; funding rounds B and C were never forthcoming, and a cash-strapped Immutep was forced to license some antibody products to GlaxoSmithKline and Novartis – after all, without money, you can't accomplish anything.

But it turned out well in the end. Immutep was acquired by Prima BioMed in 2014 – and today I'm the Chief Scientific and Medical Officer. At the time, Marc Voigt, CEO of Prima BioMed, wasn't looking for LAG-3, specifically – he was simply interested in promising innovation focused on immuno-oncology, but the GSK and Novartis deals, as well as the advanced clinical development and potential of another product, caught his eye and validated the work that we were doing at Immutep. Today, my work with LAG-3 continues at Prima BioMed and the two licensed products are progressing well in clinical trials. We also have a third product in development – IMP321 for metastatic breast cancer and metastatic melanoma. Notably, we are the first company to have a Chinese-made biological enter clinical trials in Europe and the first one presenting – just very recently – an agonist antibody to LAG-3.

Drug	*Manufacturer*	*FDA-approved indications*	*Mechanism of action*
Yervoy (ipilimumab)	Bristol-Myers Squibb	Metastatic melanoma; adjuvant treatment of Stage III melanoma	Attaches to and blocks the activity of CTLA-4
Tecentriq (atezolizumab)	Genentech	Previously treated metastatic non-small cell lung cancer; previously treated advanced urothelial carcinoma	Prevents PD-L1 on tumor cells from binding to PD-1 on immune cells
Keytruda (pembrolizumab)	Merck Sharp & Dohme	Advanced melanoma; non-small cell lung cancer; head and neck squamous cell cancer	Binds to and blocks the PD-1 receptor
Nivolumab (Opdivo)	Bristol-Myers Squibb	Advanced non-small cell lung cancer; metastatic melanoma, advanced renal cell carcinoma; classical Hodgkin Lymphoma; squamous cell carcinoma of the head and neck	Binds to and blocks the PD-1 receptor

Table1. Approved checkpoint inhibitors.

response rate. At present, achieving this level of response in metastatic cancer requires combining anti-PD1 with anti-CTLA4, which is relatively toxic.



We've only just begun

We have only scraped the surface of the potential of checkpoint inhibitors for drug development. Many people in the industry still don't really understand T cells or dendritic cells (and explaining the science to investors is always a challenge), but they do understand durable tumor regression and how important it is. The excitement and expectations for the field are having a very positive impact in terms of greater funding, even for more challenging approaches to immunotherapy, such as CAR-T cells. Indeed, the widely reported successes with CAR-T therapies have also helped to put immunology in the spotlight.

All of that said, I think immunology still deserves yet more attention. Many of the chronic diseases that the industry is desperately trying to develop treatments for can be approached from an immunological perspective. In many cases, disease is caused because of immune system regulation. Of course there are other factors that play a role too, such as genetics and external influences, but in general I believe that the full potential of immunology has yet to be uncovered and many new discoveries are waiting to be made.

In the future, immunotherapy will be increasingly broadly applied, not only in oncology and autoimmune disease, but also in neurodegenerative diseases, such as Parkinson's and Alzheimer's. There is also potential in less obvious conditions, such as atherosclerosis. Many chronic conditions would benefit from approaches that are more fundamental than merely treating symptoms. For example, could the use of statins for high blood pressure eventually be replaced by an immunology-based approach to the underlying problem?

Frédéric Triebel is Chief Scientific and Medical Officer of Prima BioMed, New South Wales, Australia.

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Bringing API Manufacturing into Focus: Lessons Learned with Brian Chekal

Brian Chekal wears two hats; one at Pfizer, where he is a senior principal scientist, and another at the American Association of Pharmaceutical Scientists (AAPS), where he chairs the Chemical and Biological API Manufacturing Technology focus group.

By Nick Miller and Stephanie Sutton

Fun teachers and practical internships can foster lifelong interest in science

When I was younger, I had a fantastic teacher called Mr Signore who had a wonderfully captivating way of bringing science to life. He would hang a giant pendulum from the classroom ceiling, hold the pendulum at the tip of your nose, and tell you to stand very still – then he'd let go! On the return swing, the pendulum would come right up to your nose, but not quite reach. With fun lessons like this, I grasped the basic concepts quickly and learned to love science. As I moved into high school, I became really interested in chemistry, leading me to do a degree and a PhD in chemical engineering.

In the summer between my undergraduate and post-graduate degrees, I landed an internship at one of Merck, Sharp & Dohme's manufacturing sites – an awesome experience! The company was trying to streamline a crystallization process, and after a few lessons and some background reading, I was tasked with trying to improve the efficiency of this procedure. It was frustrating at times because a lot of the paths I went down led nowhere, but despite that I enjoyed the methodical approach. When I first started out in the pharma industry, I already had an interest in process development – and it led to what I'm doing today at Pfizer as a senior principal scientist focused on crystallization process development. My Merck internship was in manufacturing support, but now I'm working at an earlier stage, developing the manufacturing process in the lab prior to transferring it to the commercial manufacturing site. We develop new processes rather than trying to modify existing ones, but the approach is similar.

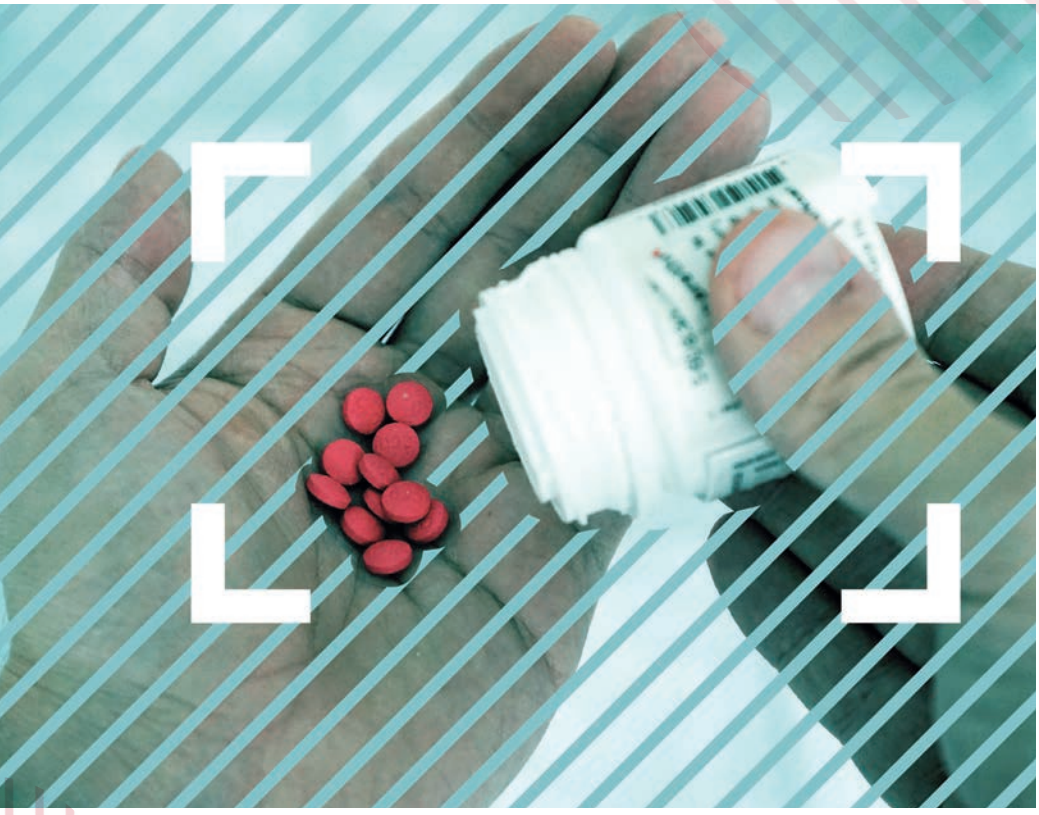
Volunteering brings rewards and satisfaction

I became involved with AAPS thanks to Cindy Oksanen – one of the senior directors at Pfizer. Cindy was involved in an AAPS section leadership at the time and mentioned that the Chemical API Manufacturing Technology focus group was looking for people to join its committee. I volunteered to serve in the group and started out as a committee member before working my way up to Chair. AAPS as a whole tends to be rather heavily drug product-centric, so we try to make our focus group a center of gravity for all the people who are more interested in the drug substance side of pharmaceutical sciences. We spend a lot of our time discussing different technologies and scientific approaches for API manufacturing processes. It's fairly small compared to other AAPS focus groups. There are around nine of us on the steering committee and the extended core of the focus group comprises around 20 people, but I'm proud of what we do. In the 2015 AAPS Annual Meeting, we had five sessions in the annual meeting program – quite a feat for a small group.

"Sharing knowledge and learning is an important goal of our group."

And it also shows the keen interest the industry has in enhancing API manufacturing processes.

One of our ambitions is to produce more webinar-based content. Not everyone can attend the annual meeting and, in any case, such sessions are only transient; webinars, by contrast, allow participation by people who can't travel



and can be made accessible on a website for years. Even if you attend a meeting, it's helpful to have the option of revisiting the same topic on a website at a later date. One very successful webinar for us was on the selection of solid forms for small molecule APIs, covering topics such as how to choose the right salt or co-crystal for development and commercialization. Solid form selection has a number of implications on the development of a new drug and requires detailed scientific understanding. We later followed it up with a webinar on the development of crystallization processes designed to achieve the desired quality attributes of the selected solid form. Sharing knowledge and learning is an important goal of our group.

Small molecules and large molecules share common ground

Originally, our group was very small-molecule centric but, based on feedback from AAPS leadership, we've since rebranded and expanded to cover large molecule APIs. Although the technical aspects of manufacturing development clearly differ between small and large molecules, the overall methodologies are pretty similar. For example, at the AAPS National Biotechnology Conference in Boston in 2016, we co-sponsored a session on the practicality of eliminating visible particles in drug products, which is a very important topic in the biologicals arena. It's also an important topic for small-molecule drugs, especially when it comes to ocular formulations or oral solutions. The source of the particles may be different, but the investigation and control strategy implementation are similar; a great deal of learning can be applied from one side to the other.

There are also a number of drugs that consist of both small and large molecules, such as antibody-drug conjugates (ADCs). ADCs are a hot topic in the industry right now, and we are looking to have more programing in the area of manufacturing of ADCs in years to come.

Continuous processing is a big topic, but we're not there yet

Another hot topic in the industry, which I am hearing about both at AAPS and during my day job at Pfizer, is continuous processing. The advantages of continuous processes have been understood for a long time and there has been intense interest in this field for the last eight to ten years. Today, we're seeing increased interest because of advances in the science and technologies. The FDA is an advocate of continuous processing and big companies, such as Eli Lilly, GlaxoSmithKline, Novartis and Pfizer, are pursuing the field with interest. I firmly believe the topic will continue to gain momentum; however, moving from batch processing to continuous processing requires changes in a number of systems and poses technical challenges. In particular, we need more work on process control to really bring continuous processing to fruition. There is also the question of skillset – few process engineers really understand how to develop a continuous process.

One of the challenges on an industry level is the fact that small-molecule manufacturing is very mature, with a large amount of capital invested in traditional manufacturing set ups. It's hard to change this infrastructure. It's a very different picture in terms of manufacturing biological APIs, where there is more investment potential; with new facilities comes the opportunity to deploy cutting-edge manufacturing technologies.

Whatever the rate of adoption, I do know that continuous processing will be discussed extensively at AAPS and elsewhere in the industry for many years to come...

Brian Chekal's Recommended Reading

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N Variankaval, AS Cote, MF Doherty, "From form to function: Crystallization of active pharmaceutical ingredients", AIChE Journal, 54, 1682–1688 (2008).

The growing power of computers will bolster manufacturing science

The continuing development and application of computational modeling tools is a very exciting area right now. At one end of the spectrum, you have very simple, but powerful, physical property models that describe vapor-liquid equilibria for predicting distillations or solid-liquid equilibria for predicting solubility. There are also mathematically complex computational fluid dynamic tools or population balance modeling tools for performing crystallization modeling. And though the tools have been around for a while, their application has been made simpler and more systematic – you no longer need to be an expert user to reap the benefits. Systems are also a lot faster than they used to be and, although this may be because of the general increase in computer speed, the overall result is much more efficient process development. Scientists can perform initial laboratory experiments, feed the data into the computational models and then run a whole series of experiments in silico; the output from the model suggests additional lab experiments, with the whole iterative process dramatically reducing development time.

Collaboration and networking promote learning

Being part of a focus group is a tremendously rewarding experience – and a lot of fun. I really enjoy having the opportunities to mentor novice scientists outside of Pfizer, especially those who are early in their API manufacturing career. The focus group has a real mix of people, from scientists who are finishing up their PhDs and keen to learn more, to seasoned industry folk and academics. Working with academics has been very interesting. Challenges in academia are different to those in industry, but at the same time we often have to solve similar problems in our daily roles. In that sense, much academic research is very relevant to industry, and it's really exciting to hear about things at the leading edge that may have industrial applications. Academics are able to go off on exploratory projects to answer interesting questions, which means there's always a possibility that they will come across something really fantastic.

"Being part of a focus group is a tremendously rewarding experience – and a lot of fun."

Over the years, we've had some really great discussions in the group. When we all come together to tackle problems, it's amazing what we can achieve.

You can find out more about the Chem Bio API Manufacturing Technology Focus Group at www.aaps.org/API_Manufacturing_Technology

Quality From the Ground Up

Six Sigma has the potential to deliver real cost savings by improving productivity and reducing defects, but making the change is challenging. Here are the essential steps to getting it right.

By Christen Davis

Minimizing variability and defects in excipients, including empty capsules, has become an increasing priority for the pharma industry. Both the FDA and EMA have developed guidance based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) quality guidelines Q8, Q9, and Q10, which cover pharmaceutical development, quality risk management, and quality systems – and since 2011, both agencies have made efforts to harmonize evaluations of the portions of applications relevant to Quality by Design (QbD).

When developing QbD programs, manufacturers must take into account the impact of raw materials on the design space, right from the start of the design process. Obviously, raw materials, including empty hard capsules – with variability small enough to avoid any significant impact on critical product or process parameters – can help avoid complications in establishing design space and obtaining regulatory approval. In line with QbD, Capsugel further tightened controls in its manufacturing facilities to produce capsules with incredibly low defect levels. In 2014, as a result of that initiative, Capsugel introduced hard gelatin capsules under a new framing reference, Coni-Snap Sigma Series capsules, which are manufactured to Six Sigma quality levels. The industry standard limit, Acceptable Quality Level (AQL), can allow for hundreds of defects per million capsules, whereas Sigma Series defect levels can reach 3.4 parts per million (ppm).

Continuous quality improvement can deliver substantial cost savings. By reducing the number of variations in manufacturing processes, you reduce inherent risk, which in turn increases turnaround speeds, allowing products to make it to market faster – and defect free. For most manufacturers, Sigma Series capsules offer the potential to improve efficiency throughout the supply chain by minimizing delays and reducing time required for acceptance testing, processing, and release – all without any need for regulatory filings or changes to the encapsulation process. In addition, good quality can result in better patient compliance since patients will come to trust a company's reputation for quality.

As our industry evolves, we must continually look for new levels of quality. We also recently moved from AQLs to Six Sigma quality levels for our Vcaps Plus HPMC capsules, in addition to our pharmaceutical gelatin capsules. We performed head-to-head trials at nearly 40 customer manufacturing facilities to test the flexibility and performance of our new capsules in filling machines under varying conditions – and found a significant increase in productivity across the board compared to previous generations. Qualitatively, the feedback we've received is that the level of quality allows companies to focus on assuring the robustness of other aspects of the encapsulation process.

Our Six Sigma processes follows the DMAIC methodology (define, measure, analyze, improve, control). The first step defines the critical quality attributes (CQAs) of product performance, which in the case of our capsules was consistent quality, Six Sigma defect levels, and superior performance on all high speed capsule filling machines. We also identified a series of control elements, including disintegration and absence of impurities, as well as superior micro, dimensional and weight consistency. After defining the specifications, we educated our raw materials suppliers on these requirements. The next step was process engineering. In any Six Sigma improvement plan, feedback during this time is crucial – it should be measured and any necessary corrective actions taken. Coni-Snap Sigma Series gelatin and Vcaps Plus HPMC capsules are now produced on redesigned and continuously evolving high-precision manufacturing and printing lines. Significant improvements in drying zone operations, with a move to high-speed machines and in-line processes, have reduced our product variations by eliminating handling steps. The capsule dipping pins were also optimized to create capsules that function well on high speed automatic filling machines and transfer systems. Finally, we developed a new process technology to ensure online electronic quality control of every single capsule, which heightened defect identification and allowed us to move to a superior quality level. We have some of the toughest product requirement specifications for manufactured capsules in the industry. The advantage is that we can pass that specificity on via a Certificate of Analysis which allows our customers to reduce incoming testing with peace of mind.

As part of continuous quality improvement, we think that customer feedback is invaluable. Reviewing our customers' performance yield and feedback for each capsule, allows us to continually evaluate the potential for variation and then work to refine our process if the capsule can solve it. I think this process makes both customers and suppliers stronger; and in doing so, reduces variation across the entire supply chain – and ultimately, the industry as a whole.

Christen Davis is Director of Quality Assurance at Capsugel, Greenwood, South Carolina, USA.

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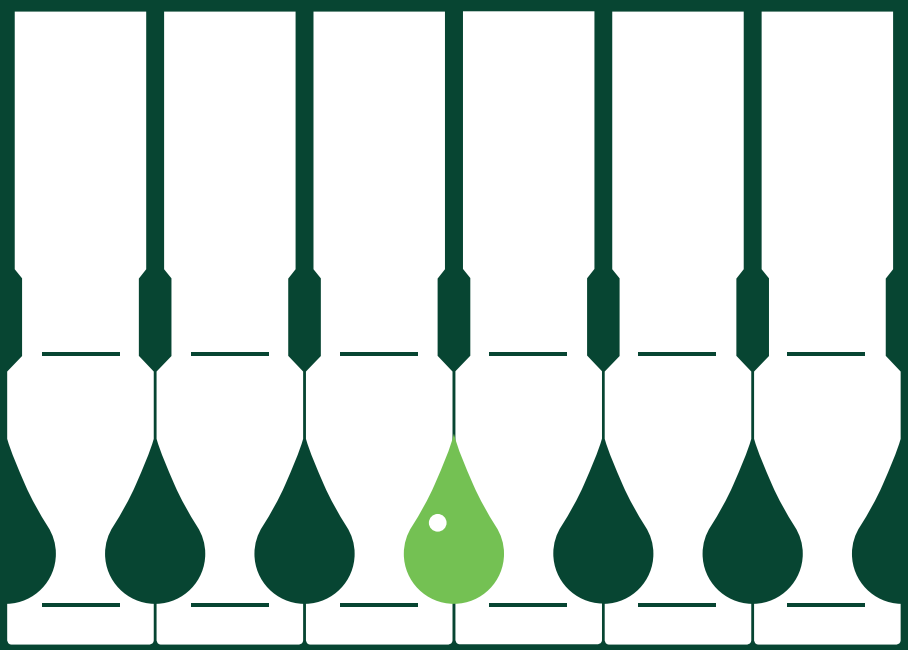


Business

Economic drivers
Emerging trends
Business strategies

Russian Revolution for Biosimilars

Biologics are expensive, but so too are biosimilars. Could local manufacturers based in Russia and other emerging markets, with their inherently lower costs, be well placed to develop cheaper biopharmaceuticals to benefit public health?

By Roman Ivanov

Many people outside of Russia do not know much about our biopharma market. In fact, the Russian pharma market is one of the fastest growing in the world – and biologics make up almost half of the Russian Federal government's spend on drugs and almost 30 percent of the overall tender market. Compared with western markets, the volume of biologics sold is small, but because of the costs of these important medicines, the burden on the country's healthcare budget is tremendous. Therefore, the government has been interested in affordable, non-original biologics for years. It is perhaps slightly surprising then that Russia did not have a specialized regulatory pathway for biosimilars until 2014.

Rise of the regulations

Prior to 2010, the regulatory environment for medicines in Russia was far from stringent – and a large number of copycat versions of epoietins, interferons, filgrastims and other biologics were launched in the country without any comparative clinical studies or comparable analytical data. On April 13, 2010, the Russian government introduced a Federal "Law on Circulation of Medicines" to better regulate the pharma industry, including both human and veterinary medicines. The law still didn't include a defined pathway for biosimilars, but there was a clear requirement for clinical trials for all drugs. Biosimilars, therefore, were treated as new biologicals and required extensive clinical testing. A biosimilars pathway was finally introduced in 2014 – and is mostly indistinguishable from the EMA's framework for biosimilars. In 2016, Eurasian Economic Union laws were also introduced whereby a drug approved in one country of the Union can be launched in all other Union members. Today, requirements for approval of biosimilar in countries of the Eurasian Economic Union are much the same as for other regulated markets.

"The big focus is on oncology biosimilars, particularly mAbs, as well as insulin and vaccines."

What often surprises outsiders is how poorly reimbursed popular anti-TNF drugs, such as Humira, Enbrel and Remicade, are in Russia – the resulting market is disproportionately small compared with other global markets. The reason for this is simply that the Russian government sees oncology, diabetes and vaccines as the priorities for healthcare expenditure. As a result, many biosimilar developers in Russia – including my own company – have steered away from anti-TNFs, even though they have been popular targets for biosimilars in other countries. Instead, the big focus is on oncology biosimilars, particularly monoclonal antibodies (mAbs), as well as insulin and vaccines because these are all well reimbursed by the government (depending on price).

At what cost

Rising regulatory requirements are important for patient safety, but there is a trade-off. The return on investment for biosimilar products in Russia is not as attractive as it was prior to 2010 because of the costs needed to meet national regulations. As a result, there are few local companies developing biosimilars or innovative biologics – most pharmacy drugs in Russia are imported. Biopharma

manufacturing is expensive in all countries and the costs are passed on to the patient and government in terms of high drug costs.

My company, BIOCAD, has invested significantly in our infrastructure to meet regulatory requirements (not an easy journey), which has enabled us to launch many biosimilars, including the first biosimilar monoclonal antibody to be approved in Russia – AcellBia (rituximab), which received marketing approval in April 2014. We've also launched products in a number of medium-regulated markets and are hoping to launch a biosimilar in the US and Europe in the future.

"The development of biosimilars is incredibly important in helping to increase access to biologic medicines."

Big international pharma companies have been very keen to capitalize on the growth opportunities in Russia and other emerging markets, and have launched a number of valuable medicines – but the high prices are a problem (this is seen on a global scale with many western markets also struggling to afford the latest biological drugs). As an industry, we know that patients need cheaper medicines, but for many companies it is hard to grant this wish. And the problem is even more pronounced in emerging markets, which have significantly smaller healthcare budgets than the US or European Union (EU) countries. Reimbursement for the most expensive biological medicines is completely impossible.

I believe that Russian companies have the potential to develop drugs cheaper than their western counterparts. For example, the cost of human resources in Russia is very low – and yet the quality of employees is high, which is a valuable factor. At the moment, I'd even go as far to say that the cost of developing a biologic in Russia is lower than in India, which is generally seen as one of the most cost-effective countries in the world for biopharma manufacture. However, the time and costs of running clinical studies, coupled with the need for significant investments in manufacturing operations, have made life difficult for local manufacturers used to the pre-2010 Russian industry.

Access all areas

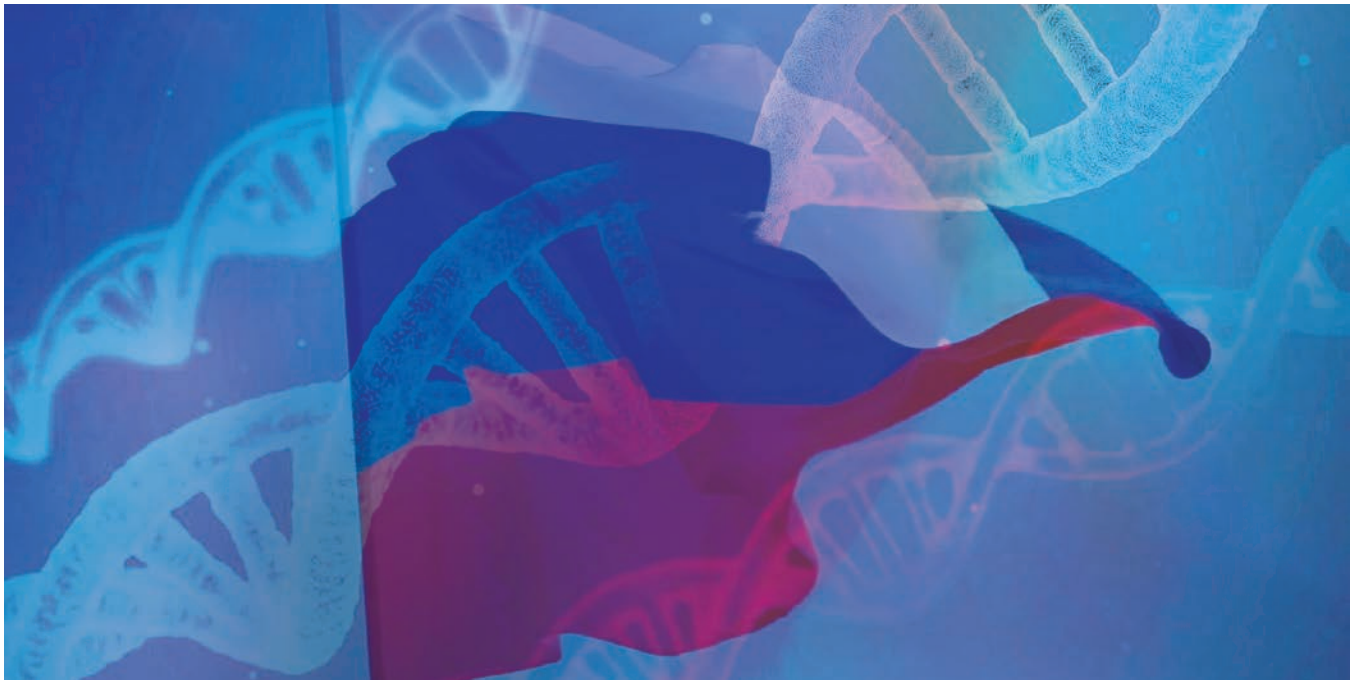
The development of biosimilars is incredibly important in helping to increase access to biologic medicines. A good example of the impact that a biosimilar can have is the drop in registered price for 400 mg of Avastin (bevacizumab). It was extremely high when it first launched in Russia – 61,536 Russian ruble, which is around US $1024 with today's exchange rate. Only a small portion of patients who needed the drug actually received it, otherwise the drug would have decimated the government's healthcare budget. In 2015, we released a biosimilar bevacizumab that was initially 30 percent less expensive. Due to price competition with the originator, the price later dropped more than 70 percent – and the number of patients receiving the treatment increased by around four times. The biosimilar changed the treatment paradigm in Russia. Another example is filgrastim. Since the launch of the first, non-original granulocyte-colony stimulating factor (G-CSF) product in 2006, the price of filgrastim in Russia dropped 70 percent in the local currency. This made the drug readily available for oncologists and it became aggressively used in modern chemotherapy regimens that require prophylactic use of G-CSF. As a result, the G-CSF market expanded 9-fold, despite the price erosion. Most importantly, it allowed more effective chemotherapy regimens to become the standard of care in Russia, improving outcomes for oncology patients.

Biosimilars of complex biologics, such as mAbs like rituximab and trastuzumab, have been approved for a few years now. They are registered or sold in dozens of countries worldwide, but access is still very limited, particularly in lower regulated markets, such as those in Latin America and North Africa. The industry is seeing some really good advances in terms of new drugs – especially in immuno-oncology – but these advances are useless if the drugs are too expensive for governments and patients to afford. From a personal point of view, I am very passionate about immuno-oncology because I focused on this topic during my university studies. Interestingly, my PhD thesis focused on CAR-T cells, but back then the technology was not well developed – neither my supervisor nor I believed that they would actually make it into the clinical setting!

I'm excited to see these therapies close to reaching the market, but it's disappointing to think that they will be unavailable to millions of patients, especially those in emerging markets. We biosimilars developers have a duty to develop not just high-quality medicines, but medicines that are affordable and available to patients who need them – in both developed and emerging markets.

The local benefit

So how do we make sure that the manufacture of biosimilars is cost effective? Large global pharma companies, such as Pfizer or Amgen, have a head start on biosimilar development, with vast amounts of funds, huge numbers of



scientists and vast experience of operating in highly regulated markets. Smaller, local companies, however, that can develop the necessary infrastructure could end up with a competitive edge over these global players. What works in western markets does not necessarily work in emerging markets and bigger is not necessarily better – particularly as the large, existing infrastructure of big pharma companies can be inflexible and difficult to update.

In my experience, it is easier to make a price-competitive biologic within a reasonable time frame if you have all the infrastructure you need in-house – and flexible, modular, single-use facilities are key. The benefits of these technologies are well known in the global biopharma industry, but such technologies are difficult for larger companies with established, stainless steel facilities to roll out, which gives newer players a competitive advantage. Single-use bioreactors and a facility that can accommodate multiple product manufacturing allow companies to extend capacity as and when required; it's very easy to bring in more single-use bioreactors to increase your output. Single use also significantly decreases capital investment, which can make a huge difference in terms of cost of goods (COGs). There are also other ways to address COGs. For example, we've developed our own critical raw materials, such as cell culture media and Protein A chromatography media. By bringing manufacturing of these raw materials in house, we've decreased COGs by several times, which helps us to be competitive in emerging markets.

Being "local" also has benefits. In Russia, for example, the government offers incentives and preferences for local manufacturers – and similar practices can be seen in many other emerging markets. If you are the only company with a specific biosimilar or biologic then being local is not quite so important, but if there is competition in the area then an international company will find it very hard to compete without a local partner. In Russia, original biologics and biosimilars are interchangeable – price is the deciding factor.

I hope that my company will have the opportunity to treat many more patients in the emerging markets – and that we can eventually bring cost-effective medicines to Europe too. Our main focus has historically been on biosimilars, but given the cost advantages of being based in Russia we believe that we can develop well-priced, innovative biologic medicines for the global market. At the moment, we have a checkpoint inhibitor monoclonal antibody in Phase 1 clinical development. Checkpoint inhibitors have revolutionized cancer treatment in the last few years, but are not as widely available as they should be, in either developed or emerging markets. And if smaller companies like mine can do something about that, you can be sure that we will!

Roman Ivanov is Vice President, Research and Development, at BIOCAD, Russia.

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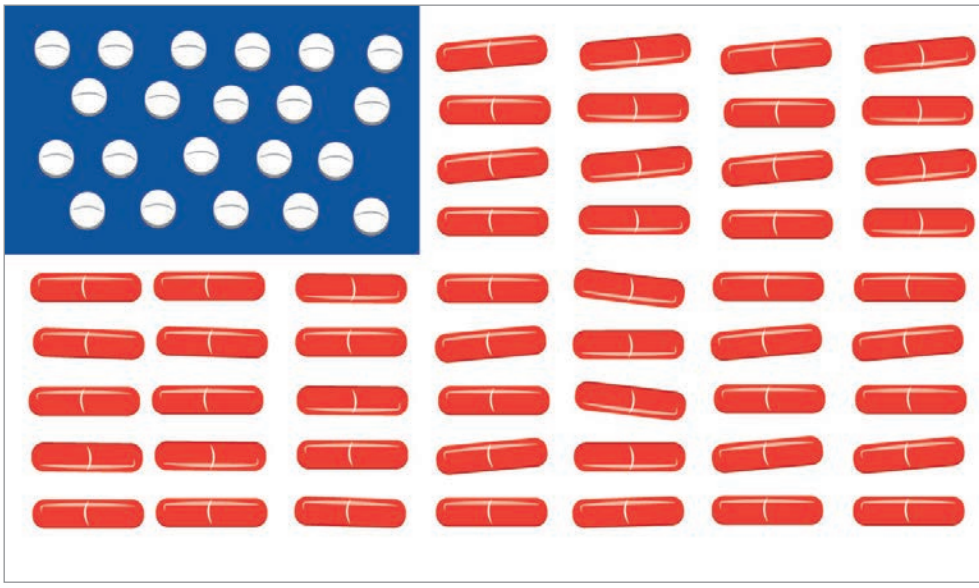
Make US Pharma Great Again!?

Donald Trump has vowed to bring down drug prices, but his policies in other areas, such as tax reforms and labor immigration, could also impact the pharma industry.

By George A Chressanthis



"And the other thing we have to do is create new bidding procedures for the drug industry, because they're getting away with murder." – Donald Trump

Since the surprise election of Donald Trump, many industries and individual companies have been on the receiving end of his comments during speeches, interviews, and tweets. At his January 11, 2017 news conference, one industry, in particular, was the target of his wrath: US pharma. The quote at the start of this article, taken from a much larger tirade against the drug industry, is typical of President Trump's recent comments against the pharma industry. Pharmaceutical and biotech stock indices, as well as stock prices of specific companies with high-priced portfolios of specialty medicines, dropped 2 to 4 percent after the news conference, on top of other previous comments made immediately after the election lamenting high drug prices (1-3).

Drug pricing, while important, is just one potential impact of the Trump presidency. His policies on areas such as regulation, taxes, international trade, and Affordable Care Act (ACA) reform could also have significant effects. This two-part series will address the following questions:

- Why has a Trump presidency targeted the biopharma industry?
- How could a Trump presidency affect the US biopharma industry through specific policy actions?
- What, if anything, can individual companies do to prepare themselves against these policy actions?
- What if any role is there for the use of commercial analytics in assisting companies to mitigate the increased risk and uncertainty caused by these policy actions?

The first two questions will be tackled in this article.

Why target pharma?

Presidential candidate Hillary Clinton and leading contender Bernie Sanders were also no fans of the pharma industry – Clinton even commented in a Democratic town hall debate that drug companies were on her most-proud enemies list, along with the National Rifle Association, health insurance companies, the Iranians, and Republicans (4). Clinton, however, received vastly more campaign contributions from drug companies relative to all rivals, including Trump, and provided high-priced speeches (though she never disclosed the transcripts of those speeches) to industry representatives (5). She represented "the devil you know" and was also more aligned with the pharma industry on international trade (the majority of growth in the global pharmaceutical market is happening outside of developed markets) (6), and was more likely to engage her adversaries in transparent and predictable ways.

A key factor complicating predictions of President Trump's effect on the drug industry is that he is not ideological, but driven by pragmatism, something Obama noted after their first face-to-face meeting at The White House (7). Also, some positions that he may wish to execute could draw opposition from his own party, particularly when it comes to drug price controls, direct federal government negotiations on drug prices, and restraints on international trade. That said, the traditional alliance that has historically prevented price controls in the US had already been showing signs of weakening before the election. The election of Trump will provide greater impetus to policy change on this issue. Trump may even find allies on some issues with Democrats, especially with progressive voters who were supporters

of Bernie Sanders. Common to Trump and Sanders voters are people who feel that the political and economic systems no longer work for them.

The pharma industry is a particularly attractive target for the populist Trump to attack for a variety of reasons:

- It is perceived as an industry headed by a few dominant global firms (even though actual market concentration metrics point to an industry that is very diffuse in market power) reaping excessive profits at the hands of those who need but cannot afford high-priced medicines.
- The industry touches everyone through the medicines people take – it is a demon everyone knows.
- There are higher cash out-of-pocket outlays for drugs relative to hospital and physician care, even though the first two comprise a far greater percentage of 2015 national health care expenditures (hospital spending 32.3 percent, professional services 26.2 percent, prescription drugs 10.1 percent [8]). Drug costs, however, are more visible to people.
- The complexity of the pharma industry makes it ripe for people to fear – it is a natural reaction to something they don't understand. Even industry insiders have a hard time explaining in simple language how, for example, drug pricing is done or the high costs and risk/uncertainties of the R&D process.
- Elderly patients on fixed incomes, representing the highest-voting participation rate population segment, are especially dependent on medicines and feel the economic hardships when drug prices rise.
- Actions by bad industry actors, such as illegal sales and marketing practices, and price gouging of old generic drugs, fuel populist anger at the industry. Despite a variety of medical advances from the industry that benefit society, low Gallup polling data taken over time on the industry reflects this anger (9).
- The news media and medical journal establishment are all too willing to engage in what one author has called "pharmaphobia" in demonizing the industry (10).

The uncertain ride

In the sidebars on pages 47 and 48, I have tried to predict (based on content from his website) the policies that President Trump may take on a wide variety of issues and then extended these to the areas that could impact the overall business performance of the US pharma industry. Some policy actions are predicted to have a positive impact on pharma (see sidebar on page 47), such as intellectual property protection and tax/financial reforms, whereas others, such as policies on drug pricing, labor immigration and international trade, are likely to be more negative (see sidebar on page 48).Each sidebar is not meant to be a comprehensive list, but rather a prediction of key areas that have a possibility of occurring. Empirical analysis is needed to understand the magnitude of potential policy action effects.

Trump's victory highlights the growing trend of populism, which has been seen in other countries in different forms. The common themes are public reactions to growing economic inequality, people who have been marginalized in society and resistant to social change, and attacks on well-entrenched political, economic, or cultural institutions that many people see as no longer working for them (11). Based on this thesis (and similar explanations) of the factors causing the rise of Trump's brand of populism, the pharmaceutical industry is especially ripe for ridicule and attack. The pharma industry is well-connected in the political system and seen as one of the most powerful lobbying groups in the halls of government. The industry is also seen as an economically powerful sector and pharma companies are placed in the difficult position of arguing that for-profit enterprises require the current price structure to stay in business. Companies would not stay in business very long if they supplied medicines for free (or nominally priced) to all those who could not pay for them. Currently, the pharma industry is losing the optics battle, even if real world evidence is on its side.

My concern is that the pharma industry is in for an even more uncertain ride than it was expecting before the election of President Trump. It would be wise for industry executives not to dismiss the significance and implications of his victory. The long list of not only defeated Republican and Democratic presidential candidates, but also the repudiation of political, economic, social, and media elites, are testimony to the dangers of underestimating this populist movement. For the pharma industry, a clear rethinking is needed of the commercial model. As has been stated in a previous article, there is the growing gap between the rising cost of pharmaceutical R&D to bring drug innovation to the market and individual/societal willingness and ability to pay for this innovation (12).

The next article in this two-part series will look at what pharma companies can do to mitigate the increased risks and uncertainties brought about by a Trump presidency, as well as analytics to help redefine a commercial model design.

George A Chressanthis is Principal Scientist at Axtria. This article has been co-published with Axtria: www.axtria.com.

The references for this article are available in the online version at www.themedicinemaker.com.

Potential Positive Impacts on Overall Industry Performance

Intellectual Property Protection

Strengthen intellectual property (IP) protection in developing countries.
Many developed markets like the US, Japan, and some European countries have strong IP protections. However, China, India, Canada, and other nations have far weaker regulations. Weak IP protections mean less innovation, which in turn decreases patient access to new medicines and reduces health/economic outcomes (13, 14).

Tax and Financial Reforms

Reduce the US corporate income tax rate to be in line with or lower than major OECD trading countries
The proposed lowering of the tax rate from 35 percent to 15 percent would significantly decrease the financial incentives for merger and acquisition activities driven by tax inversion/transfer pricing effects (as studied in a prior white paper [15]), repatriate profits held in oversea subsidiaries for reinvestment in the US for R&D, and use for productive acquisitions and/or payouts to shareholders (16).

Enact a deemed repatriation of corporate profits held offshore at a one-time tax rate of 10 percent
Coupled with a significant reduction in the corporate income tax rate, this added inducement will further repatriate overseas profits for reinvestment in the US and will benefit a number of pharma companies.

Maintain the corporate tax expenditure for the R&D credit (neutral impact)
While many changes are expected on corporate tax policy, such as the elimination of virtually all tax expenditures, the tax credit for R&D investment is proposed to be maintained. This added financial incentive is important for the research-intensive pharma industry.

Eliminate the virtually unique US practice of citizen or resident-based taxation on global personal income
US citizens or resident aliens pay taxes on global income, regardless of whether they are living in the US or abroad. The US practice of citizens or residential-based taxation is virtually unique from the norm of territorial-based taxation, where only income from a source country is taxed by that country. Such a change would make it easier for companies with US citizens or residents who work for biopharmaceutical multinationals to operate in foreign subsidiary units.

FDA/Regulations

Reduce federal regulations, which are seen as impediments to business
Some regulations will be reviewed in order to expedite the approval of both innovator drugs and generics. This could have a mixed positive and negative impact.

Clarity on review of business operations outside the US
Clarity on data integrity, compliance with cGMPs for overseas operations, self-monitoring quality and manufacturing processes, and advancing mutual reliance agreements for GMP inspections with authorities in Europe and elsewhere should help companies.

Crackdown on quality control of business operations in China and India for drugs utilized in the US
President Trump intends to make it more difficult for businesses to produce drugs outside of the US, such as in China and India, for domestic consumption. If the policy intent is to enhance quality controls for drug manufacturing operations, then that's a good thing. If, however, the policy intent is simply to "tax" producers of drugs outside the US for domestic consumption, then it will have a negative impact on businesses and potentially start a trade war, which could adversely affect other positive impact policy actions.

Increase resources to the FDA to reduce chronic staff shortages
Improved resourcing will help staffing to work on new drug approvals, generic-drug applications, and expedited applications.

Funding of the 2016 Cures Act
Signed into law in in December 2016, this bipartisan-approved act aims to support research for rare diseases, new approaches to streamline the drug approval process, the use of RWE in support of new indications, and increasing the focus on patients in drug development.

Potential Negative Impacts on Overall Industry Performance

Drug Prices

Establish a bidding process to allow the federal government to directly negotiate drug prices with drug companies for Medicare patients

The adverse consequences to pharma R&D investment, new drug innovation, and future beneficial effects on health/economic outcomes would be significant, as examined in a prior article (13). New drug pricing for Medicare would not happen in a vacuum; it would likely spill into and lower commercial plan prices, thereby establishing a lower "best commercial price" and even lower Medicaid pricing.

Allow US consumers to import drugs from foreign markets, thereby putting even greater pressures on pricing in the US market

This policy change is perhaps less likely to occur. Legally, re-importation of drugs can already occur, provided such drugs are certified as meeting FDA quality control standards and supply chain safety assurances of non-tampering and non-counterfeiting.

Affordable Care Act/Medicare Reform

Improve patient access to quality healthcare through ACA reform

The potential impact of this is uncertain. The process of "repeal and replace" Obamacare is still ongoing, and details as to what the replacement will be are not yet known. One patient group that has definitely benefitted from the ACA is the poor. For pharma, however, Medicaid is high-volume/low-margin business and also forces generic drug utilization to limit costs, which is negative for pharma.

The ACA has crowded out some small employer-based health plans – and whether employees have received access to better quality healthcare and improved drug coverage under the ACA is debatable. My estimate is that reforms to the ACA will lower the cost of accessing healthcare by eliminating mandated services that people do not need, enable plans to be sold across state lines (thereby increasing risk pools and competition), and allow for high deductible plans that were in effect before the ACA and worked to lower healthcare spending. Whether this results in improved access to drug plans that allow for greater spending on branded medicines remains to be seen.

Mandate greater use of generic and biosimilar drugs for Medicare patients

This policy approach would be consistent with Trump's comments about leveraging the buying power of the federal government to lower drug costs for people – and would be negative for innovator drugs.

Labor Immigration

Restrictions on the issuance of visas for high-skilled immigrants

On his campaign trail, President Trump noted that the country's H-1B visa program was being abused by companies and was bad for American workers. Restrictions on the visa program would limit pharma companies' access to skilled workers if they cannot fill vacancies with American workers. Many biopharma consulting companies, such as those in the commercial analytics space, also use high-skilled workers from India and China, and have major off-shore operations in India. Restrictions placed on these organizations may prevent them from operating effectively, generating adverse effects for biopharma clients.

International Trade

Increase in policies that promote protectionism and possible trade war conflicts

President Trump's "America first" philosophy will be clearly seen in his trade policies, reviewing and demanding revisions of multinational trade partnerships, such as NAFTA, while already nixing the TPP deal, to proposing a border tax for companies who leave the US and then send foreign-produced products back to the US. We will likely see tougher trade stances against the EU, China, and other countries that Trump feels have taken advantage of the relatively more open US market, while also making it difficult for American companies in foreign countries to do business.

The fear is a trade war and lower overall world prosperity, which will reduce global patented branded and biologic drug demand (while increasing generic and biosimilar demand). For biopharmaceutical MNCs, heightened global protectionism will make for more difficult business practices, and less freedom to operate where it makes more sense from an efficiency standpoint. Normally, the costs of such protectionism policies results in higher domestic prices, but with controls planned on drug prices, companies will be less able to cost-shift the effects of trade policies. Next overall effects will be to lower margins for companies, reduce R&D investment and opportunities for expanding the volume of business.

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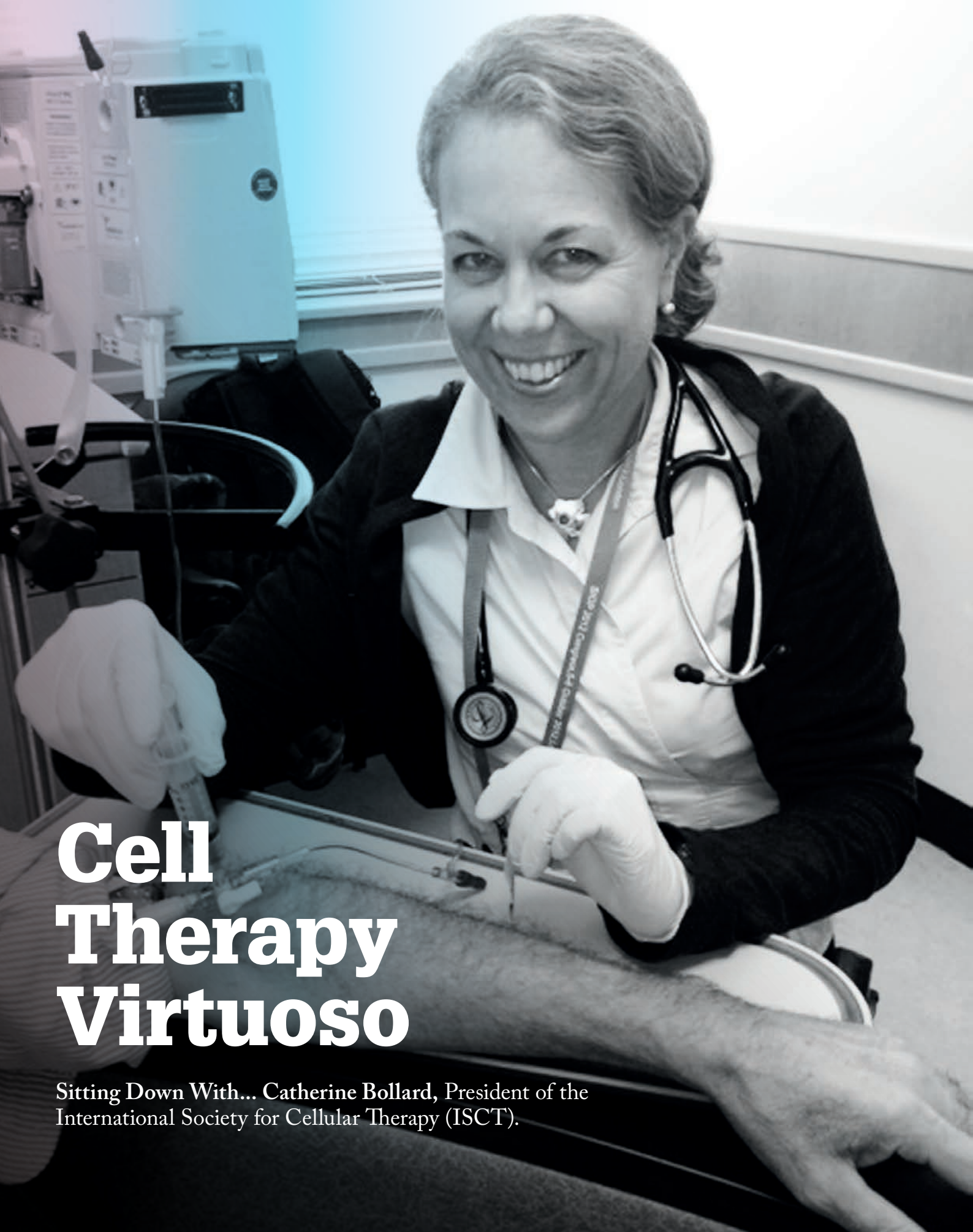

Cell Therapy Virtuoso

Sitting Down With... Catherine Bollard, President of the International Society for Cellular Therapy (ISCT).

What inspired you to follow a medical career?

When I was 18 years old, I had to decide between medical school or opera singing. I chose medicine, thinking that I could revisit singing after qualifying – and I continued my voice training throughout medical school. After obtaining my medical degree, I moved to London to continue my opera training at Guildhall. But my husband was a musician too, and it was hard for a couple of poor musicians to live in London! I did a locum at St Bartholomew's in pediatric hematology and oncology – and I absolutely loved it. One day, when I was exhausted after being on call for 96 hours, my music teacher told me that I had to give up medicine. Medicine or singing? It was heart-wrenching, but I opted for medicine. I still keep up the music as a hobby – and I think the characteristics of a good doctor are similar to those of a good musician: one fixes the body and the other mends the soul.

How did you become interested in cell therapies?

In the 80s, my best friend in high school, Diana, developed Hodgkin's lymphoma. Treatment comprised multiple cycles of chemo- and radiotherapy, but finally she went into remission. Later, she was diagnosed with myelodysplastic syndrome – a direct consequence of the Hodgkin's therapy – and died soon afterwards of leukemia. It was so cruel, and it became clear to me that we needed therapies that only kill the cancer cells and not healthy bystander cells. As a result, I became interested in cellular immunotherapy.

My mentor in New Zealand was friends with Helen Heslop and Malcolm Brenner – two leading immunotherapists at Baylor College of Medicine in Houston, USA – and I agreed to work with them on neuroblastoma. But when I arrived, the neuroblastoma post-doc decided to stay on, while another (who had been working on Hodgkin's lymphoma) left, so I was able toon lymphoma – one large focus of my career ever since. We've now developed a T-cell therapy that gives complete remissions in over 50 percent of some patient groups, and two-year progression-free survival rates of over 90 percent in other groups. Cell Medica is taking this product to licensure. It's exciting, but also very sad. If Diana had been diagnosed today, her outcome would have been completely different.

How did you get involved with ISCT?

When I was at Baylor, my boss, Dr Brenner, was President of ISCT so of course he encouraged us all to join! I really enjoyed its bench-to-bedside philosophy and the fact that it encompassed all aspects of cell therapy. I became President in 2016.

What is ISCT's current focus?

ISCT's mission is to "drive the translation of cellular therapies for the benefit of patients worldwide" and to "improve patients' lives through safe and effective cellular therapies". At the moment, we're very focused on maximizing our growth in terms of membership, as well as reaching out to the community through current and new collaborations. As new cell products become available, I would like to see ISCT support the IND-enabling studies that bridge "the valley of death" – the early phase studies where success is critical for generating corporate interest and later phase licensing studies.

What are your goals for 2017 as President of ISCT?

In recent years, the society has enhanced its regenerative medicine profile, and I now wish to build its profile in immune cell-based therapies, especially in cancer immunotherapy. 2017 marks ISCT's 25th anniversary and I'm hoping to engage past-ISCT presidents – who were the early drivers of cancer cell therapy – to re-energize this arm of ISCT.

The ISCT also has a responsibility to help younger professionals develop the necessary skills to contribute to the field. Training the next generation of cell therapists is a passion of mine; in 2015, I helped develop an intensive cell therapy training course with the American Society of Blood and Marrow Transplantation. The first course was very successful so we're doing another this year.

What do you think will help to further advance the field?

I'd like to see more collaboration between pharma companies – not only in terms of developing a given cell therapy, but in the development of combination treatment strategies utilizing immune and cell based therapeutics. For example, if cancer is to be cured, it will most likely require immunotherapy combinations, which will require this sort of collaboration. ISCT is well-positioned to facilitate collaboration between pharma companies as our commercialization committee has developed close working relationships with industry and academia.

What are the most exciting changes you've seen in the cell therapy field?

The field has expanded dramatically over the last 25 years. In particular, T-cell therapies for cancer have grown rapidly and now the field is expanding into other areas, such as regulatory T-cells for autoimmune disease and virus T-cells for HIV. Given what the immune system can do, the applications are almost limitless. Technological advances now place this diverse array of treatments within reach of generalizability. Ongoing issues include the question of whether we should have centralized or decentralized GMP facilities – or perhaps even a "GMP in a box" approach where blood and reagents go in and your product comes out!

ISCT will celebrate its silver jubilee at its upcoming annual meeting on May 3-6 in London, UK. Visit http://isct2017.com/ for more details.

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