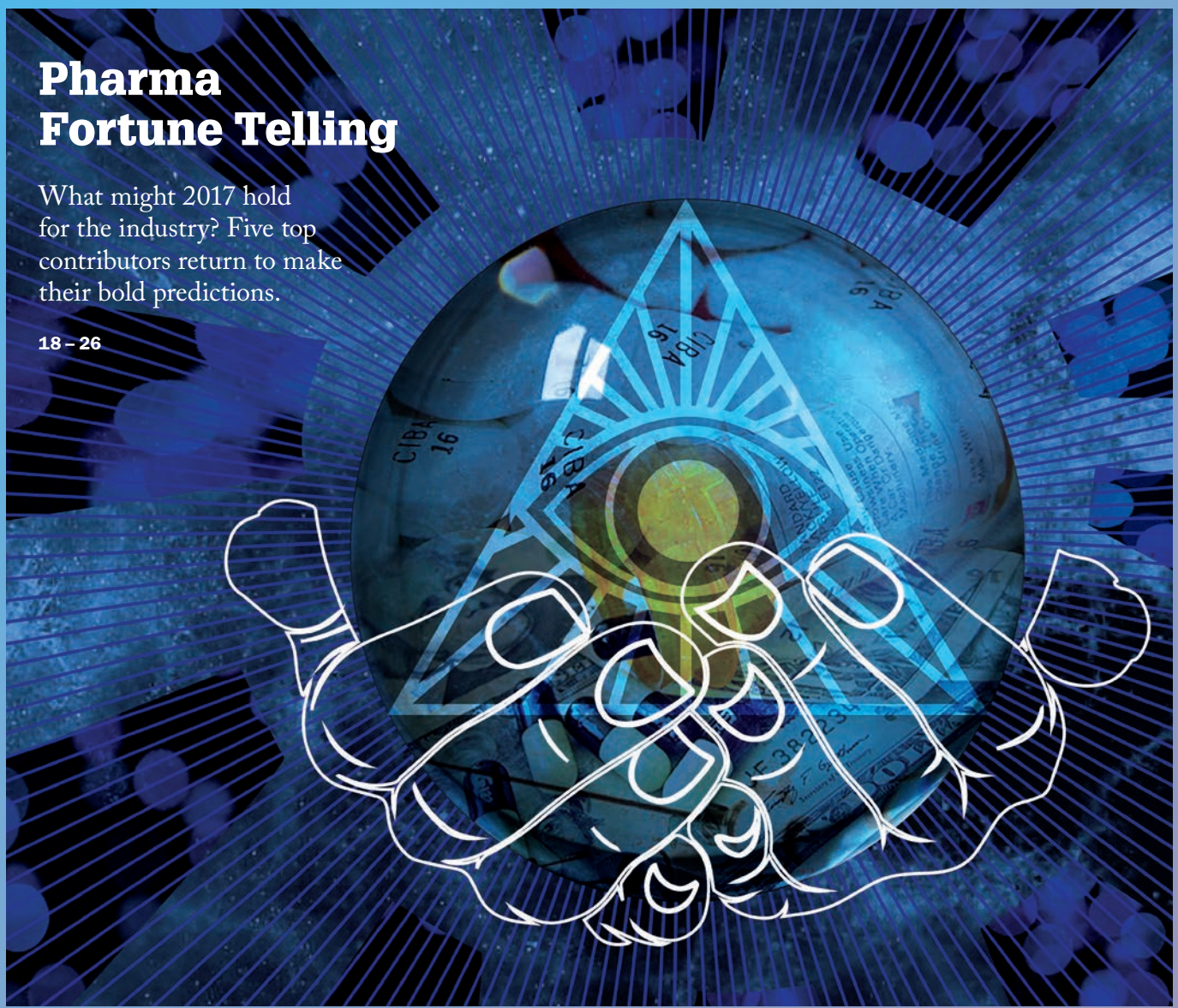
JANUARY 2017 # 26

the Medicine Maker



Pharma Fortune Telling

What might 2017 hold for the industry? Five top contributors return to make their bold predictions.

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Erena Sawyer-Wagner
Analytical Chemist
Analytical Development

Online this Month

Last call for nominations for the 2017 Power List!

The deadline for The Medicine Maker 2017 Power List is nigh – nominations will close on February 1, 2017.

This is your last chance to nominate someone for this prestigious list. Have you been inspired by a brilliant mentor? Do you know a ground-breaking scientist who deserves recognition? Has a colleague pulled off a highly successful project?

The Medicine Maker Power List will celebrate the best and the brightest that the drug development and manufacturing community has to offer – from business leaders, to entrepreneurs, to consultants, to drug development experts and more. The best part is that it's up to you to choose the experts you want to be considered for the list.

Any and all nominees will be considered by our expert judging panel and the final list will be published in April 2017.

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

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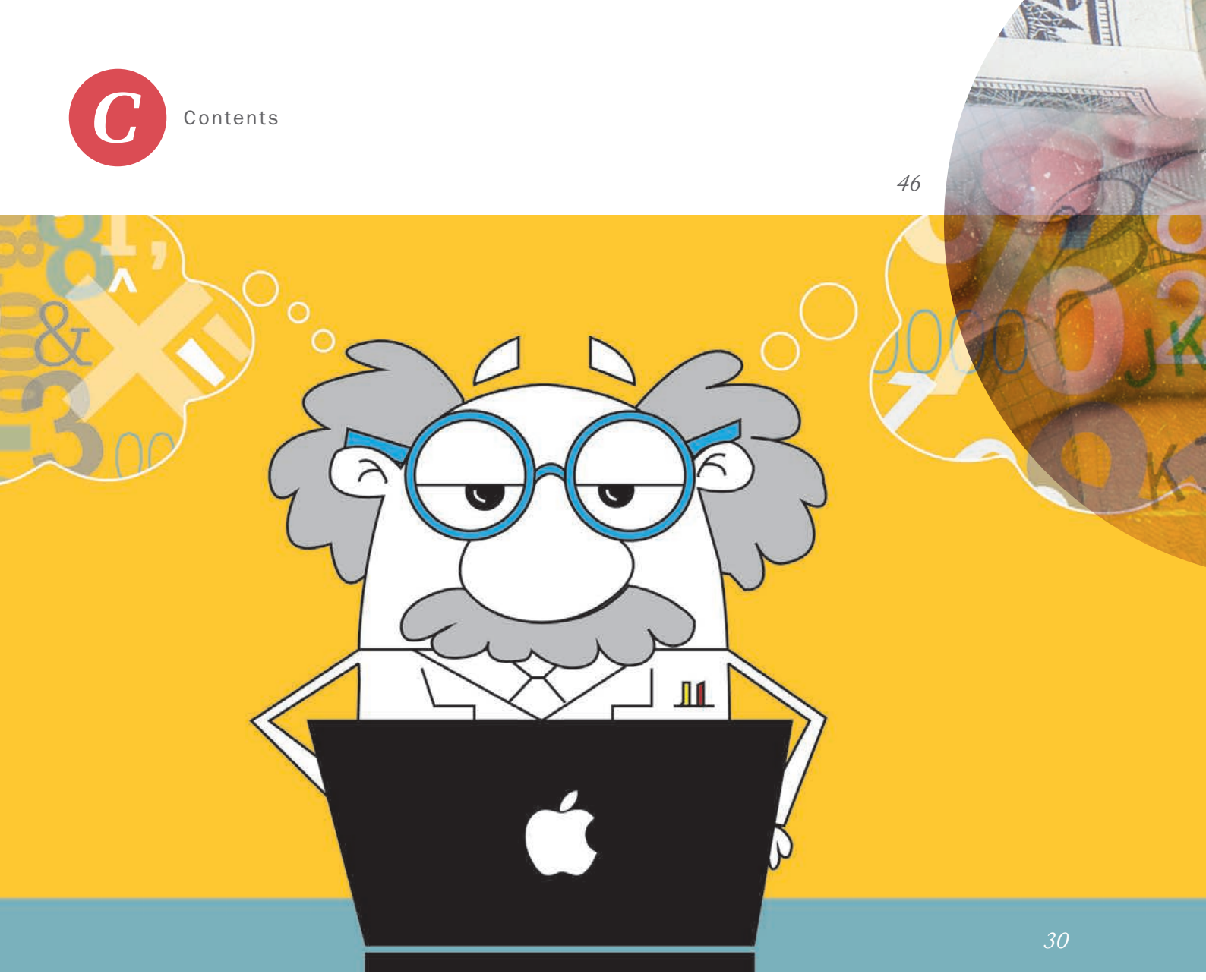

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Failure to Engage

Could public health suffer if the pharma industry doesn't learn how to win back trust?

There is a growing disconnect between pharma manufacturers and consumers. An example of this is highlighted on page 10: 37 percent of patients do not know who manufactures any of their medicines. Will consumers engage with or trust a company if they are unaware that it benefits them – or their friends and family – directly? Experts contributing to our cover feature on page 18 suggest that educating consumers could help, but given the public's distrust of pharma, improving the relationship quickly may prove to be a herculean task. But if pharma doesn't find a way to win trust, public health could suffer.

In January, President Trump met with Robert F. Kennedy, Jr – a well-known anti-vaccine activist. Kennedy claims he's been appointed to chair a commission on vaccination safety and scientific integrity – information that has been denied by a spokesperson from the Trump transition team. That said, Trump has previously expressed concern about vaccinations and a link to autism – and met with another anti-vaccine activist (and disgraced UK doctor), Andrew Wakefield, during his presidential campaign.

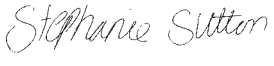
What these meetings could mean for vaccination and the vaccines industry is unclear. But if we've reached the point where activists appear to have more clout with the President on a public health issue than the scientific community, it's time to worry.

The pharma industry certainly tries (and has the potential) to educate patients about health issues such as vaccination, diseases awareness, and the dangers of buying medicines from unregulated websites. But it will be less successful if it is considered in any way untrustworthy; consumers may simply see marketing campaigns in disguise...

So how can the industry win back trust? One way is to get involved with local charities or the community, supporting endeavors outside the realms of medicine. Many companies are already doing this, but the work is often not well publicized, which is a shame because it shows that pharma has a genuine and open interest in promoting health and wellbeing. I recently read that Morningside Pharmaceuticals – a small company based in Loughborough, UK – donated money to help fund a minibus that will be used to reach isolated elderly people living in the area. It's not a glitzy million-dollar donation, but there is no doubt that it will have an immediate and positive impact on the local community. And it proves that the pharma industry has a heart – perhaps the best way of changing negative perceptions.

If your company is involved in a charitable initiative that deserves a little more attention, please get in touch. We'd be happy to share pharma's altruistic side.

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

Relating the Geno to the Pheno

Health data analytics seek to unravel the biology behind Alzheimer's and Schizophrenia

Finding links between genetic markers and the end phenotype can be difficult – especially with complex diseases, such as Alzheimer's and Schizophrenia, where a multitude of other environmental factors affect disease development. In an attempt to close the gap, researchers from the University of Pittsburgh and Pfizer have announced a collaboration that aims to create a statistical model that relates brain scan data to genetic profiles (1). We spoke with Kayhan Batmanghelich, principle investigator and Assistant Professor in the Department of Biomedical Informatics in the School of Medicine, to tell us more about the collaboration.

How did the collaboration come about?

The idea for the collaboration stemmed from conversations I had during my post-doc at MIT. Pfizer happened to have an office close to where I worked and, one day, I bumped into one of their researchers. We got chatting and decided that it might be a good idea to work together.

What is the goal of the collaboration?

When people do Genome Wide Association Analysis (GWAS), there are so many things that happen in between the genetics and the diagnosis – and one of the modalities that can fill that gap is imaging data. When you image brain anatomy, you measure the variation in the tissue. For example, in Alzheimer's disease, we know that the cortical thinning and loss of gray matter tissue in areas related to the memory area manifest as the symptoms of the disease. Now, with MRI images we can measure this and use it as a surrogate for the disease. The idea is to take the variation data from the MRI scans and relate it to the underlying genetic and clinical observational data, with the ultimate aim of developing an algorithm that explains causal relationships between them. We hope it will provide a deep insight into the underlying biology of the diseases.

Why collaborate?

In recent times, the budget of the NIH has remained constant while the number of scientists has increased, meaning that budget per capita has decreased. It's important to think outside the box to obtain other sources of funding. When we presented the project to Pfizer, they confirmed that they had similar issues that needed resolving. Why not combine resources and make things more efficient? I think there's a trend towards greater openness and collaboration in research that will inevitably lead to more innovation on the industry side, as well as greater opportunities for academia in terms of funding.

What are the main challenges when collaborating with industry?

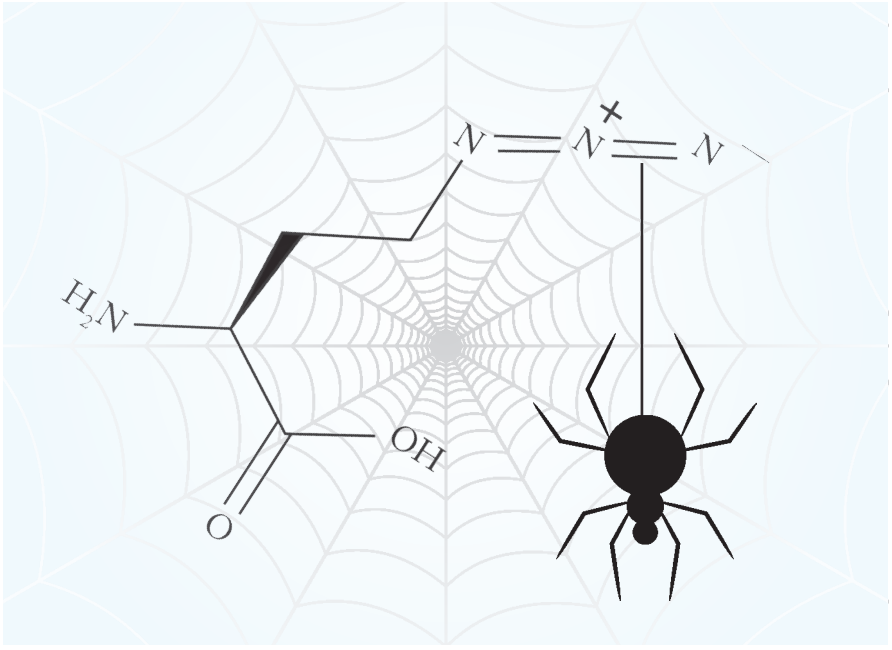
In general, when you're working with pharma there can be strings attached to the data in terms of restrictions on publication. It's understandable, but if industry wants to work with academia more frequently, there will need to be a more relaxed approach. On the university side, there can be a tendency towards protecting intellectual property and I think that could also be a little more relaxed to encourage collaboration with industry.

Reference

1. *University of Pittsburgh, "Pitt, Pfizer Team Up on Health Data Analytics", (2016). Available at: http://bit.ly/2juQnHX. Last accessed January 11, 2017.*

Oh, What a Wonderful Web We Weave

Could chemically functionalized spider silk be used for innovative drug delivery?



Spider silk has been used in medical settings for millennia – going back to the Ancient Greeks and Romans who applied cobwebs directly to wounds (1). References to spider silk are dotted throughout history and even make an appearance in Shakespeare's Midsummer Night's Dream, "I shall desire you of more acquaintance, good Master Cobweb… If I cut my finger, I shall make bold of you." Scientists have known for some time that some spider silks have antibiotic properties, along with remarkable ductility and tensile strength – comparable with that of high-grade alloy steel.

It was these properties that intrigued Neil Thomas, Professor of Chemistry at the University of Nottingham, UK, when he attended a "sandpit" event designed to bring academics together from different disciplines. "There, I met Sara Goodacre [Assistant Professor in the School of Life Sciences at Nottingham] who was talking about the low-level antibiotic properties of natural spider silk," says Thomas. "I realized that we could produce spider silk based on the '4RepCT' protein – a miniaturized spider silk protein originally developed by a group in Sweden – and modify it to include reactive groups in specific positions, which we could then modify with fluorescent molecules, antibiotics or other drugs."

The chance meeting five years ago culminated in the publication of a recent paper (2). The group found that the silk could be modified with the unnatural amino acid L-azidohomoalanine – which replaces the L-methionines in the silk proteins – this introduces the azide group which is reactive under very selective conditions without changing its fiber-forming self-assembly properties. In addition, they found that drug molecules or fluorescent molecules could be "clicked" onto the silk proteins either before or after assembling the fibers. If this is done in batches with different antibiotics, the batches of modified silk proteins can then be mixed and self-assembled into fibres decorated with different antibiotics in a known ratio, to help fight antimicrobial resistance where a cocktail of different antibiotics is often used.

"We attached the antibiotic levofloxacin to the silk via a linker with a chemical bond that is sensitive to acidic pH or enzymes released by bacteria," says Thomas. "As bacteria grow, their local environment becomes slightly more acidic over time, and the chemical bonds between the silk and the antibiotic breaks – slowly releasing the antibiotic and killing the bacteria."

The researchers envisage the chemically-functionalized spider silk being used to deliver drugs or heal wounds. "We think the main current use, once further testing and optimization has taken place, may be in diabetic ulcers and other slow-healing wounds," says Thomas.

The silk is generated in bacteria, which has advantages for scale-up and sustainable manufacture. "A recently published pivotal paper (3) from a group working on a similar spider silk system reported being able to spin 1km of silk per liter of bacteria with little additional processing," says Thomas. *JS*

References

1. *BM Godfrey, "Traditional and modern biomaterials science uses of spider webs", (2016). Available at: http://bit.ly/2iFai6P. Last accessed January 11, 2017.*
2. *D Harvey et al., "Antibiotic spider silk: site-specific functionalization of recombinant spider silk using 'click' chemistry", Adv Mater (2016). PMID: 28028885.*
3. *M Andersson et al., "Biomimetic spinning of artificial spider silk from a chimeric minispidroin", Nat Chem Bio, 2269, (2017).*

A Bad Relationship

Our infographic highlights the disconnect between patients and drug manufacturers

Inspire's annual survey – involving more than 10,000 patients – revealed that almost 40 percent of patients have no idea who makes the drugs they take (1). Moreover, the survey found that only 14 percent of patients feel like they have a relationship with the pharmaceutical manufacturers behind their drugs – and of that, under half reported having a "good" relationship.

On a more positive note, the study also shows that patients are taking a more active role in their treatment. For example, 52 percent of respondents initiate the discussion about new treatment options when speaking with their physicians. Increasing numbers of patients are also using their smartphones to manage their healthcare, and many patients are actively interested in getting involved with new medical innovations around gene testing. *JS*

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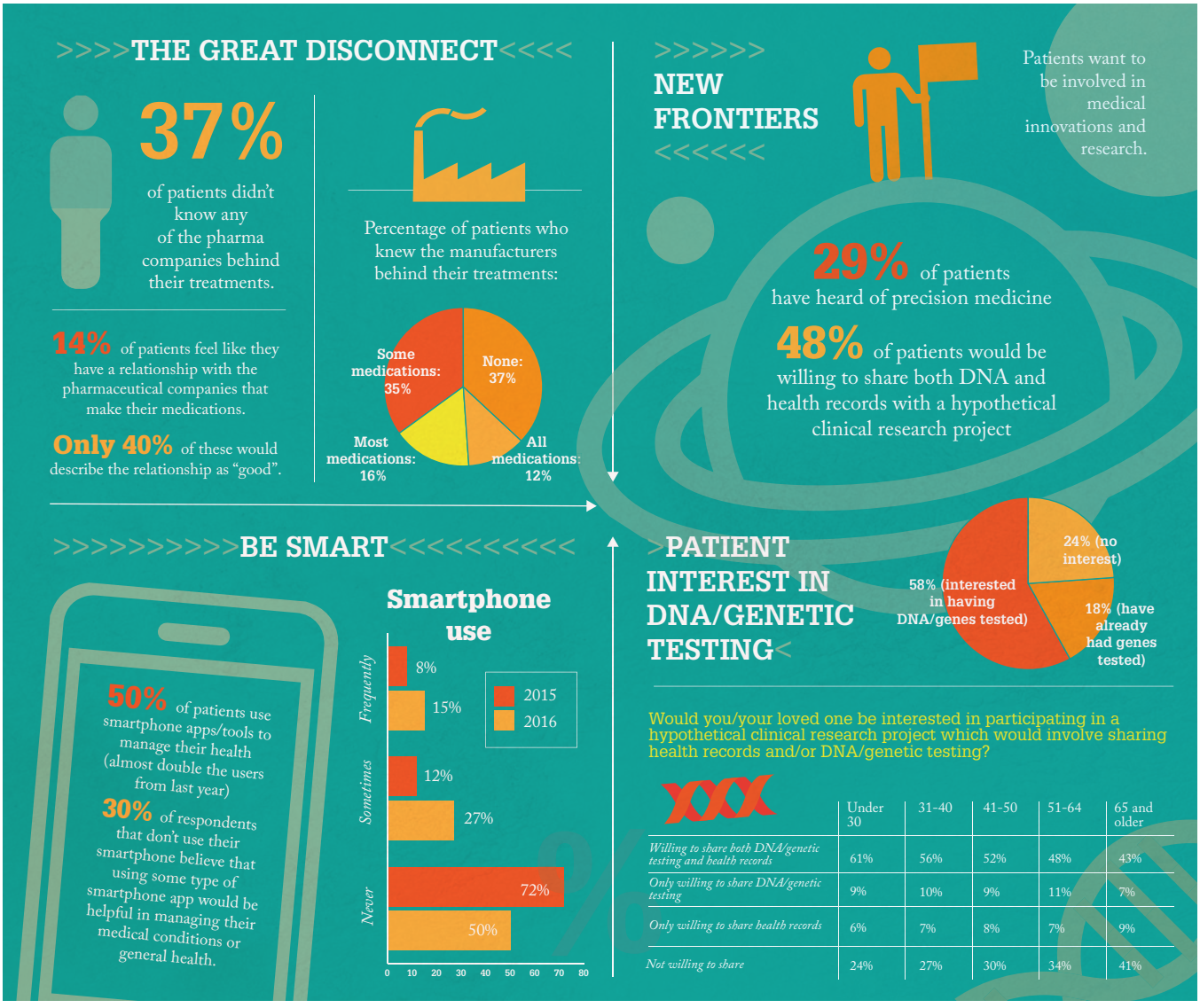
1. *Inspire, "Insights from engaged patients," (2016). Available at: http://bit.ly/2juQxPn. Last accessed January 11, 2017.*



	Under 30	31-40	41-50	51-64	65 and older
Willing to share both DNA/genetic testing and health records	61%	56%	52%	48%	43%
Only willing to share DNA/genetic testing	9%	10%	9%	11%	7%
Only willing to share health records	6%	7%	8%	7%	9%
Not willing to share	24%	27%	30%	34%	41%

Trump Targets Pharma

"We're going to start bidding," says Trump. Could Medicare price negotiations be on the cards?

Pharma stocks were sent tumbling after Donald Trump targeted the industry in his first press conference in seven months. "We have to create new bidding procedures for the drug industry because they're getting away with murder," he said.

"New bidding procedures" could be a reference to Medicare price negotiations, which both Trump and Hillary Clinton had advocated during the election campaign as a means of curbing drug prices (as discussed previously in The Medicine Maker [1]).

Medicare is a national social insurance program, mainly for the over 65s, and Part D of that program subsidizes the costs of prescription drugs and prescription drug insurance premiums for Medicare beneficiaries. However, because of a "non-interference" clause, the Secretary of Health and Human Services is prohibited from interfering in the private price negotiations between Medicare Part D plans and drug manufacturers. Although (unlike Clinton), Trump did not explicitly advocate repealing the "non-interference" clause, he did say that Medicare could "save $300 billion" a year, if it negotiated discounts.

In the press conference, Trump revised his savings estimate saying, "We're going to start bidding and we're going to save billions of dollars over a period of time." In our feature in September (1), we argued that Trump and Clinton were actually remarkably close on pharma, both agreeing that action is needed to bring down rising drug prices and even agreeing on specific policies. Indeed, Trump may face much stiffer opposition from his own party who have historically opposed Medicare price negotiations – including his pick for head of the Department of Health and Human Services, Representative Tom Price, a Georgia Republican.

In the press conference, Trump also criticized pharma for moving manufacturing operations out of the US. "We have to get our drug industry coming back," he said. "Our drug industry has been disastrous. They're leaving left and right. They supply our drugs, but they don't make them here." Trump has said he will slap a hefty border tax on goods exported back to the US to encourage companies to manufacture their products in the US.

Following Trump's comments, the S&P 500 healthcare index dropped 2 percent, before rallying slightly. The Nasdaq biotechnology index sank 4 percent, the worst since June 24 – the day after the Brexit vote. *JS*

Reference

1. *J Strachan, "The great American debate", 5, 20-27 (2016). Available at: http://bit.ly/2eiyB8i*

Business-in-Brief

A patent surprise, authorization denied, and EpiPen's monopoly compromised... What's new for pharma in business?

Regulation

- Amgen has won a major legal victory in its patent battle with Sanofi and Regeneron over the companies' competing high cholesterol drugs, likely securing control of the still promising PCSK9 market. In a surprise decision, a federal judge granted Amgen's request for a permanent injunction against Sanofi and Regeneron, effectively banning sales of their drug Praluent – which is currently used by patients – in US markets. Sanofi and Regeneron said they will appeal the ruling and seek a suspension of the injunction during the appeals process.
- The FDA has awarded fast-track designation to Astellas' DNA vaccine candidate for peanut allergies, which is designed to mitigate severe hypersensitivity reactions caused by peanut allergy. The news comes alongside the prediction from a senior analysist that EpiPen will lose $800 million in sales to generic rivals by 2018.
- The US Senate Special Committee on Aging has released a report that lays out strategies to prevent pharma companies from buying old off-patent drugs and then making profits by charging massively inflated prices. The Committee provides a number of potential policies to end the practice, including incentivizing generic competition and temporary drug importation. (Drug costs are also an issue disused in this month's feature on page 18)

Politics

- Outgoing US Vice President Joe Biden is reportedly set to head up a new non-profit organization to tackle a broad range of cancer issues – including high oncology drug prices. Biden, who led the Obama administration's Cancer Moonshot, has reportedly said that he wants to begin a national conversation and get Congress and advocacy groups on board to make sure cancer treatments are accessible for everyone.
- Donald Trump is "exploring the possibility of forming a commission on autism," according to transition spokesperson, Hope Hicks. The statement was made following a meeting between the Trump team and Robert F. Kennedy Jr., a proponent of the widely discredited theory that vaccines cause autism. Kennedy told reporters that he had been offered a position heading up a commission analyzing vaccine safety. The trump team however denies the claim, stating: "no decisions have been made at this time."

Manufacturing

- AstraZeneca has opened a £120-million biologics plant in the UK to manufacture oncology drugs. The plant was officially opened in December by CEO Pascal Soriot. However, AstraZeneca have said that the plant will not create any new jobs at the site, where the company already employs around 3,000 workers.
- The European Medicines Agency has suspended the manufacturing authority of Danish repackager EuroPharma after finding serious breaches of compliance with GMP during an inspection in December. Inspectors say that EuroPharma falsified the expiration dates on products and sold products from contractors whose sites had never been audited for compliance, among other problems. The regulator has already recalled any products that may have been affected.

For links to original press releases, visit the online version of the article at: www.themedicinemaker.com/0117/business

Parents Pass Placebos

Is it ethical to use placebo controls in pediatric clinical trials? Most parents say, "yes"

The ethics around placebos have been discussed for some time in the medical community, but it's an even more hotly debated subject when it comes to clinical trials involving children, despite evidence suggesting that placebo effects in pediatrics are significant. Clearly, children require special consideration and a trial can't go ahead without parental consent, so it's important to understand what parents think.

Until recently, data has been lacking but now researchers from Harvard Medical School have conducted a survey to assess parental attitudes regarding placebo usage in pediatric, randomized controlled trials and clinical care (1). "Our aim was to further understand the obstacles related to children enrolment in a placebo randomized controlled trial and to understand the feasibility of clinical opportunities, such as placebo therapy, which can maintain the therapeutic benefits and decrease the use of medication with potential side effects," said Vanda Rocha Faria, lead author of the study and Research Fellow in Anesthesia at Boston's Children's Hospital.

The researchers found that the majority of surveyed parents considered the use of placebos acceptable in both pediatric care (86 percent) and pediatric trials (91.5 percent), while only 5.7 percent of parents reported the use of placebos in children as unacceptable. Respondents' judgment and acceptance were influenced by the doctors' certainty about the therapeutic benefits of placebo treatment, the pediatric conditions for placebo usage (mostly psychological), transparency, safety, and purity of placebos.

Interestingly, the researchers also found that more than two-thirds of parents would rather have their child enrol in a clinical study to test the effectiveness of a new drug against a placebo without pharmacologic side effects than in a study testing the new drug against an already existing drug with possible pharmacologic side effects. Most parents also indicated that they would like to be informed about clinical trials results and, if results suggest that certain drugs do not work better than placebo, do not believe it acceptable for a doctor to prescribe those drugs to children.

"In out study, we found that parents seem to be quite positive towards placebo use," says Rocha Faria. "However, if deception is involved, then their attitudes change."

Rocha Faria also pointed out that a number of parents spontaneously left positive comments at the end of the survey. "Some said they would like to read more on the topic, others that they would like to see our recommendations implemented in clinical practice... I think it shows there's a genuine interest in the topic." *JS*

Reference

1. *V Faria, "Parental attitudes about placebo use in children", J Pediatr [Epub ahead of print] (2016). PMID: 27863847.*

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

Biosimilars, Come Fly With Me

Let's follow the tune of the airline industry and cooperate to de-risk investments, optimize costs, and maximize sales.

By Catherine Godrecka-Bareau, Global New Products Director – Biosimilars, at Merck KGaA.

Seven out of the top ten drugs are biologics. All will lose patent protection by 2020, representing an underlying pool of $60 billion in branded sales to grab for biosimilars. Are biosimilars the new El Dorado of the pharma industry? If only it was that simple to strike gold! The biosimilars market is a challenging business, where players have to deal with high R&D costs, unclear regulatory pathways, and uncertainty around business models.

First, let's review the key characteristics of the biosimilars game. To play, large investments are required; companies need to invest $150-300 million over an eight-year time frame just to come up with a valid biosimilar compound. Next, a further $50-100 million is needed to set up reliable manufacturing capacity – unless the player can leverage existing biologic manufacturing capacity.

On top of the minimum investments, players have to deal with many uncertainties, particularly in the US. The US accounts for half of the opportunity today, but regulatory pathways are still being clarified. For example, there are no clearly defined provisions for interchangeability or substitution, and although indication extrapolation may be possible, it is still uncertain. Additionally, originators are filing lawsuits to block or delay the entry of biosimilars, and there is still a need to further educate payers and the medical profession about the safety and benefits of biosimilars. Finally, it is unlikely that any one player will be able to offer a one-stop shop with a complete portfolio of all the biosimilars. Fragmentation will force providers to source from many players, which means duplicative efforts to source the biosimilars versus if a player could offer all the biosimilars at once.

In my view, biosimilars companies could learn a thing or two from the airline industry when it comes to de-risking, optimizing costs, and maximizing sales. Before 2000, each airline was "flying solo" across the entire value chain of the business; for example, each company had their own procurement, maintenance and repair, booking system and frequent flyer program. In the year 2000, however, the airline industry was hit by a major crisis – skyrocketing oil prices. Plus, the advent of the Internet allowed consumers to easily compare prices online, which eventually led to a price war and a downward spiral of profitability. Finally 9/11 brought le coup de grace as traffic drastically decreased in a matter of months with public fear of flying.

The airline industry has survived and, indeed, flourished. One of the main problems plaguing the airline industry was waste in terms of duplicated efforts between the different airlines. Part of the solution was consolidation – many companies merged while others went bankrupt. The second part was collaboration and improved efficiencies. American Airlines led the initiative with the creation of One World, which comprises 16 permanent partner airlines. Lufthansa led the second biggest alliance, with Miles & More, which comprised 13 permanent partner airlines. These alliances allowed contributing partners to share procurement; for example, pooling the purchase of airplanes led to

bulk discounts. Each alliance has a shared center of excellence, leading to substantial economies of scale in maintenance, repair and booking systems. Finally, each alliance offers a pooled frequent flyer program, incentivizing passengers to fly with airlines within the alliance.

So what can the biosimilars industry learn from the airline industry? First of all, it is important to review the development chain for biosimilars since this will allow us to see where costs occur and where further investments are needed. I believe that there are six areas of investment for any biosimilars player:

- R&D, including cell-line and process development, reference material sourcing, analytics and manufacturing/scale-up.
- Manufacturing. This step is directly linked to the first step, as process development and the manufacturing scale-up should preferably be examined early on.
- Regulatory. It is critical to obtain FDA and EMA green lights. The US and Europe account together for over 70 percent of the total biosimilar potential.
- Market access. It is not sufficient to put a product on the market. The drug also needs to be made available from payers. Establishing strong payer relationships is key to ensure the drug gets on the formulary and gets reimbursed.
- Marketing. There is a need to adopt a branded mentality to win stakeholder trust – it's an expensive commercial approach to build from scratch unless the player has prior biologic experience.
- Intellectual property. This is an important element that should span every other step. It's advisable to invest in an in-house legal team to ensure no valid patents are infringed throughout development. It also implies significant investment in legal battles to neutralize originators' defense strategies against biosimilars.

In my opinion, the players who master these steps will be best equipped to master the biosimilars environment.

At the moment – just like the airline industry in 2000 – the biosimilars industry is duplicating efforts and under-utilizing assets. Players are working in silos. For example, there are over 20 companies working on a biosimilar of Humira. Instead, we could (and should) be building alliances and partnerships that allow us to leverage asset utilization. Why can't we collaborate on sourcing reference materials and aligning standards for analytics?

But what would such a collaboration look like? First, there would need to be at least three companies in the cooperation and data would need to be shared not as a package, but as and when they become available. Finally, outsourcing general analytical characterization for each partners' compounds would be helpful since it would decrease the amount of cross-validation. In this context, a firewall between the participating companies would be crucial so as not to destroy the competition and to equalize the timing.

The bottom line is that to turn the biosimilars opportunity into sustainable success, it must be profitable – and that could well mean working together.

The Perfect Package

Are current guidelines around packaging and product degradation suitable for real market conditions?

By Ajith Nair, Senior Vice President, Pharma Packaging Solutions, Global PPI for Bilcare Research.

We all know that medicinal products require protection from environmental variables that accelerate degradation – namely, moisture, light and oxygen. And

though the common stability guidelines established by the International Council for Harmonization (ICH) cover the basic requirements for stability studies, I find them rather general in nature and not always well-matched to real-world market circumstances. Often, the guidelines lead to after-the-fact stability studies of packaged products performed to validate – rather than shape – the primary packaging process.

Today, many packaging solutions are able to prevent or retard efficacy loss, and advanced computer simulation and study tools can subject products to rigorous evaluation. By considering a product's moisture, light and gas barrier requirements (along with its physical dimensions), it is possible to design packaging that passes stability testing – and to do so cost effectively.

Despite the availability of solutions, why are packaging optimization tools not in widespread use? A number of obstacles exist. Understandably, pharma companies tend to pay more attention to drug development than drug stabilization. Following years of expensive research, development and clinical studies,

companies are always eager to get their product to market. To that end, the stabilization documentation required by regulatory bodies is often handled via the path of least resistance. And that means that most drugs are actually over-packaged. Although erring on the side of caution may seem like a good idea, it's a waste in terms of cost. On the other hand, failing to fully understand your product's packaging needs can also lead to problems in more challenging environments, such as very hot and humid climates.

Regulatory guidelines are purposefully broad; it is simply impossible to list and address each and every potential scenario. Recognizing this, regulatory bodies are now advising pharma manufacturers to do their homework in terms of understanding the specific stability challenges of their products in real-life market challenges. The FDA has issued a guideline that encourages quality, safety and efficacy controls to be incorporated into the production process that adhere to Quality by Design principles (1).

Though this is a step in the right direction, I believe that greater regulatory oversight could – and should – be put into place, particularly as so many technologies to aid packaging optimization are so readily available. One reason for the delay in rolling out such technologies is that medicines – particularly tablets and capsules – are often packaged differently depending on the country they will be sold in. In many parts of the world, solid dose medicines are packaged directly in unit dose format in approved manufacturing sites under clean and controlled environments. They then travel through the supply chain in their original packaging until the last pill is consumed by the patient, all of which helps ensure product stability. However, in the USA, the initial validation process is essentially eradicated all too often. Products typically go through multiple re-packs to suit bulk packaging supplies of pharmaceutical producers. Consumers often receive their 30- or 90-day pill prescription in vials – and it's amazing how often these are stored in bathrooms or kitchens, which offer far-from ideal conditions for storage in terms of temperature and humidity! Such vials are opened and exposed to environmental conditions daily, which can potentially limit product potency. Medicines are not usually tested against this level of exposure.

It's not easy to change supply chain infrastructure or end-consumer practices, but some companies are waking up to the problem and I am seeing a movement towards more protective unit dose packaging in the US, such as blister packing with barrier protection.

Although ICH stability studies do not adequately address real-life environmental supply chain challenges faced by pharmaceutical products, they remain the basis for FDA product market approval. It is time for that to change. Pharmaceutical scientists, packaging experts and regulatory authorities must come together to formalize a better drug stabilization approach that will benefit the entire pharmaceutical community – including patients.

Reference

1. *FDA, "Quality by Design for ANDAs: An Example for immediate-Release Dosage Forms", (2012). Available at: http://bit.ly/2j5GX8M. Accessed January 11, 2017.*

Standing Up for Microcalorimetry

Modern microcalorimetry certainly has great potential in biopharma development but, to make the most of any technique, it is important to understand its advantages and limitations.

By Natalia Markova, Principal Scientist – MicroCal, at Malvern Instruments.

Making sure you have an optimal set of analytical techniques at your disposal is crucial whatever your research focus, but can be particularly challenging in sectors that are experiencing rapid change, such as biopharmaceutical development. Biopharmaceuticals and biosimilars are still relatively young drugs when compared to their small-molecule counterparts – and as readers know, they can behave unexpectedly during manufacture.

The biopharmaceutical sector has been climbing a steep learning curve, but at last we are gaining a better understanding of which properties to monitor and how to measure them. That said, there is still room for improvement. Today, the main concerns in drug development focus on bioactivity and efficacy, stability, ease of delivery, safety and immunogenicity. What (and how) to measure when it comes to understanding these factors is still open to debate, especially as requirements can change throughout the drug development pipeline. Instrument manufacturers continue to work hard to commercialize new technologies to meet the industry's modern needs – and today there are many analytical solutions to choose from.

Techniques that can stay the course from formulation through to manufacture are highly desirable. In my view, orthogonality – the application of alternative techniques

based on different measurement principles – is essential to secure understanding and provide the thoroughness needed to progress through development with confidence. Biopharma development is already expensive and mistakes waste precious resources.

One technique that I think is underutilized in the industry is microcalorimetry. Microcalorimetry involves the measurement of the very small heat changes that occur when a drug interacts with a target site or a protein unfolds, for example, and can help deliver information about those interactions and behaviors. Modern microcalorimetry instrumentation can detect temperature changes of as little as a millionth of a degree, which allows users to observe and quantify changes with just 10 µg of sample. But how should the biopharma community apply the technique to get the best (and most useful) results?

With isothermal titration calorimetry (ITC), heat changes are measured when a ligand, such as a drug candidate, is progressively added to a biomolecular target. The resulting heat profiles generate a wealth of information that can be used to understand molecular interactions, aiding hit selection and lead optimization. ITC, therefore, lends itself to drug discovery.

In contrast, differential scanning calorimetry (DSC) detects protein unfolding/conformational change triggered by the application of a temperature ramp, thereby quantifying stability. Stability is a defining issue throughout biopharmaceutical development through to the point of drug delivery – from early screening through to quality assurance and control, and for biosimilar development. The value of the data provided by DSC therefore remains high throughout the drug pipeline.

DSC can usefully accompany a biopharmaceutical product from its earliest origins all the way to the shelf. Instrument developers must ask themselves how best to adapt DSC technology to meet requirements at every step. Current systems consume relatively little sample and are automated for higher sample throughput – important benefits, of course, that fit the technique for screening applications. To realize DSC's broader value, however, we need to ask some searching questions:

- How can we analyze DSC data as precisely as possible to maximize sensitivity?
- How can we accelerate and "deskill" the analytical process to make DSC more suitable for the manufacturing environment?
- How can we streamline DSC to dovetail seamlessly with orthogonal techniques, such as dynamic light scattering, which also have an established role in stability assessment?

If we can answer these challenges, DSC will be able to deliver to its full potential and build on its role as a constant companion throughout drug development and into commercial manufacture. However, more generally, these two examples highlight the need to really understand the potential of a technique to fully exploit its value. ITC boosts productivity primarily by generating a wealth of information to accelerate a single step of development – drug discovery – while DSC is a core tool across the development cycle. I believe we need to explore and embrace techniques in both camps to develop biopharmaceuticals safely and effectively.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REVELATIONS AND RESOLUTIONS

It seems likely that 2016 will go down as one of the most eventful years in modern history, but what did the pharma industry make of it? Here, we quiz a number of past contributors to The Medicine Maker for their opinions on 2016 – and ask them what priorities and resolutions the industry should focus on for 2017.

By Stephanie Sutton

What were the highs of pharma's 2016?

Markus Thunecke: For me, three things stand out. First is the continued success story of immuno-oncology – in particular, there was much new data revealed in the field of checkpoint inhibitors and cellular therapies. Secondly, gene therapy may finally deliver after decades of ups and down – promising real breakthroughs in the field of genetic diseases, such as retinal dystrophies, beta thalassemia or haemophilia B. Thirdly, though the number of FDA approvals was lower in 2016 compared with previous years, there are positive signs in company pipelines. The value of the top 30 pharma companies' pipelines has increased considerably over the last 2-3 years (based on analyst consensus valuations). When one compares this value increase with R&D spending over a longer period, we get a genuine increase in R&D productivity. Some companies, including Gilead, Celgene or Biogen, have outperformed the rest, but I think that many other big pharma companies have learned important lessons on how to better recognize and capture innovation externally. As one example, although the checkpoint antibody revolution was initiated in academia and smaller companies, it's Bristol Myers Squib and Merck, Sharp & Dohme who pushed it across the finishing line.

Christa Myers: The Zika virus was a large part of the overall world health story in 2016. Everyone worried about the health of their Olympic athletes in Brazil and the possibility of the spread of the virus. The silver lining was that it led to much more activity in the pharma industry to support this important neglected disease. And the research and development will not only address the concerns of this virus, but also drive knowledge for other insect-borne diseases, vaccine development, and testing capabilities. We also increased knowledge of our own immune responses during pregnancy for the mother and the developing fetus.

John Talley: I was really pleased to see a number of industry success stories in terms of anti-cancer efficacy, particularly with regards to checkpoint inhibitors. In the US, recent congressional approval of the "21st Century Cures Act" may have a favorable impact on early stage research into more ambitious disease targets, such as central nervous system diseases, infectious diseases and cancer. The bill is intended to streamline the grant application process, as well as the clinical and regulatory pathways.

Eva McLellan: I also believe that advances and approvals regarding immune-oncology have been high points. 2016




Featuring

Markus Thunecke

Founding Senior Partner at Catenion, Berlin, Germany.

Markus is a biochemist turned strategy consultant. In his early career, he developed transgenic rodent models for Alzheimer's disease before turning his attention from mice to humans. After two stints at larger consulting firms, Markus focused on his passion for biopharmaceutical innovation by founding Catenion together with three like-minded partners in 2003. "I've often observed that within large organizations the most interesting breakthroughs happen in spite of rather than because of a particular strategy or organizational setup. This is a typical starting point for an R&D transformation effort."

Christa Myers

Senior Pharmaceutical Engineering Specialist at CRB, USA.

Christa has an extensive background in the design of fill-finish facilities, chemical kilo labs, pilot plants, API research and manufacturing facilities, bulk pharmaceutical chemical facilities, highly hazardous compound containment and biotech process facilities. Her involvement starts with the strategic concept and continues through construction and startup of projects. "My role is to provide clients with insight as to how innovative technologies apply to process and facility designs."

John Talley

Chief Scientific Officer, Euclises Pharmaceuticals, USA.

An organic chemist by training, John Talley is responsible for discovery and preclinical development of new chemical entities at Euclises Pharmaceuticals, Inc. His research examines the role of prostaglandins in immune suppression within the tumor microenvironment. "I am particularly interested in the utility of prostaglandin synthesis inhibitors to enhance the efficacy of checkpoint inhibitors by boosting immune control of tumors."

Eva McLellan

Regional Disease Area Director, Oncology Pipeline at Hoffmann La Roche, Basel, Switzerland.

Eva McLellan (née Furczon) is responsible for the commercial strategy of Roche's early oncology pipeline in Europe. Her industry experience spans operational and strategic responsibilities at the affiliate, regional, and global level and includes roles in field sales, medical affairs and marketing. "I am passionate about innovation. I love to integrate people, perspectives and creative approaches to help teams navigate complex and evolving environments."

saw several FDA approvals of checkpoint inhibitors PD-1 and PDL-1 for multiple indications, including lung cancer. These new therapies offer transformation potential rather than incremental improvement. In addition, I was excited to see CRISPR-Cas9 – the potentially industry-changing gene technology – enter human clinical testing. I also have an interest in biosimilars, so I was pleased to see biosimilar monoclonal antibodies, such as Inflectra, being approved by the FDA. Why is this a big deal? Well, because it means that patients have even more access to lifesaving drugs in both emerging and developed markets. It also means that we will have more competition in the marketplace, which will further push the boundaries of innovation. Though a status quo is fine in certain industries, innovation is extremely important in pharma and very good news for patients and society as a whole.

And the lows?

MT: Business models that solely exploit pricing inefficiencies of public and private healthcare systems for their own "enrichment" are a low point – such companies rely on profit maximization models without investing in innovation or adding anything meaningful to global healthcare. For a while, these "no internal innovation investment models" were very popular with investors (and consultants who sometimes became CEO), but it is my firm belief that our industry has an ethical obligation to invest in innovation as long as it benefits from the social contract through public healthcare funding.

CM: The fraudulent pricing practices of a few companies in 2016 has put undue pressure on the entire industry – and weakened public trust in pharma. I think companies need to better highlight the great work they are doing to help save patients money. For example, new equipment and processes being used in industry have been designed for higher throughput and lower manufacturing costs, which in the end should help bring the cost of medicines down.

JT: I think it is disappointing that the industry has failed to make any progress in terms of the pharmacological intervention in the

Biopharma's Bright Future

The National Institute for Bioprocessing Research and Training (NIBRT) recently published a survey of 2016 trends in biopharma (1).

Overall level of optimism for future growth?

69% Highly Optimistic

Only **4%** neutral or pessimistic

Technologies expected to offer the biggest benefits in the future

The biggest challenge of developing new drugs is the scientific complexities in discovering effective therapies for unmet medical needs.

The biggest challenges in manufacturing?

- Process robustness
- Reproducibility of process
- Product yield optimization

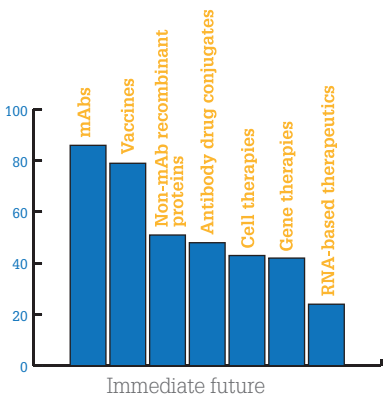
Manufacturing areas ranked as "high priority for further innovation" by respondents

Cell line development and optimization – **67%**

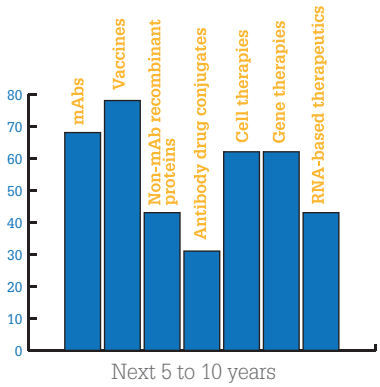
Bioanalytical capabilities – **61%**

Downstream processing – **59%**

Commercial products ranked as "highly important" by respondents



Immediate future



Next 5 to 10 years

And what about talent?

57% of respondents have difficulty in recruiting bioprocess engineers

42% have difficulties recruiting for downstream processing roles

(1) NIBRT, "2016 Trends in Biopharma Survey Results" (2016). Available at: http://bit.ly/2jaDJkn. Last accessed January 12, 2017

Words of Wisdom for the New Year

Markus Thunecke:

"There are a number of companies in the race to test gene editing in clinical settings. If a therapeutic application showed real benefit with acceptable safety in a clinical setting, it could lead to an unprecedented wave of innovation – although it is hard to predict when this will happen, as safety and specificity are still concerns. Almost inevitably, most potential breakthrough innovations go through a long cycle of ups and downs before they finally deliver."

Christa Myers:

"2016 was a year of Olympics, political change and celebrity deaths, but the true heroes in our world are not athletes, politicians or celebrities. The heroes in our world are the unsung technical people in hospitals, laboratories and manufacturing facilities who are striving to find new treatments and cures for people. If you ask the families of those people affected by medication or treatment how much impact you have had – they will tell you that the makers, inventors, developers, engineers, and so on, are worth all of the money in the world because you gave them hope for their loved one."

Eva McLellan:

"Disruptive technologies and artificial intelligence (AI) are transforming business models in all industries. Companies like Uber and Airbnb own no vehicles or real estate but are the world's biggest market places in their respectively industries. This is where I think the next wave of innovation in healthcare is eventually headed. Imagine the largest hospital network that owns no hospitals. Imagine a doctor and patient interaction revolutionized using AI and machine learning. IBM's Watson technology is already being used to help healthcare practitioners make treatment decisions, diagnosis disease, and understand compliance. In 2017, we will just begin to scratch the surface of this type of personalize care, but it's starting to happen and the potential impact is game changing."

treatment of Alzheimer's disease. The industry must continue to explore new treatment modalities for Alzheimer's and, at the same time, make a concerted effort to more fundamentally understand the underlying causes of this devastating disease.

EM: I think it is always disappointing when promising drugs do not meet their primary endpoints. The industry had a few of those in 2016. These are sobering reminders that it's just how science works... In these cases, the industry should do what any good scientist would – get curious and analyze the results to look for insights, and then share them with the industry for the benefit of all. Such a gesture could help inform the many other ongoing trials and ultimately accelerate future success for patients.

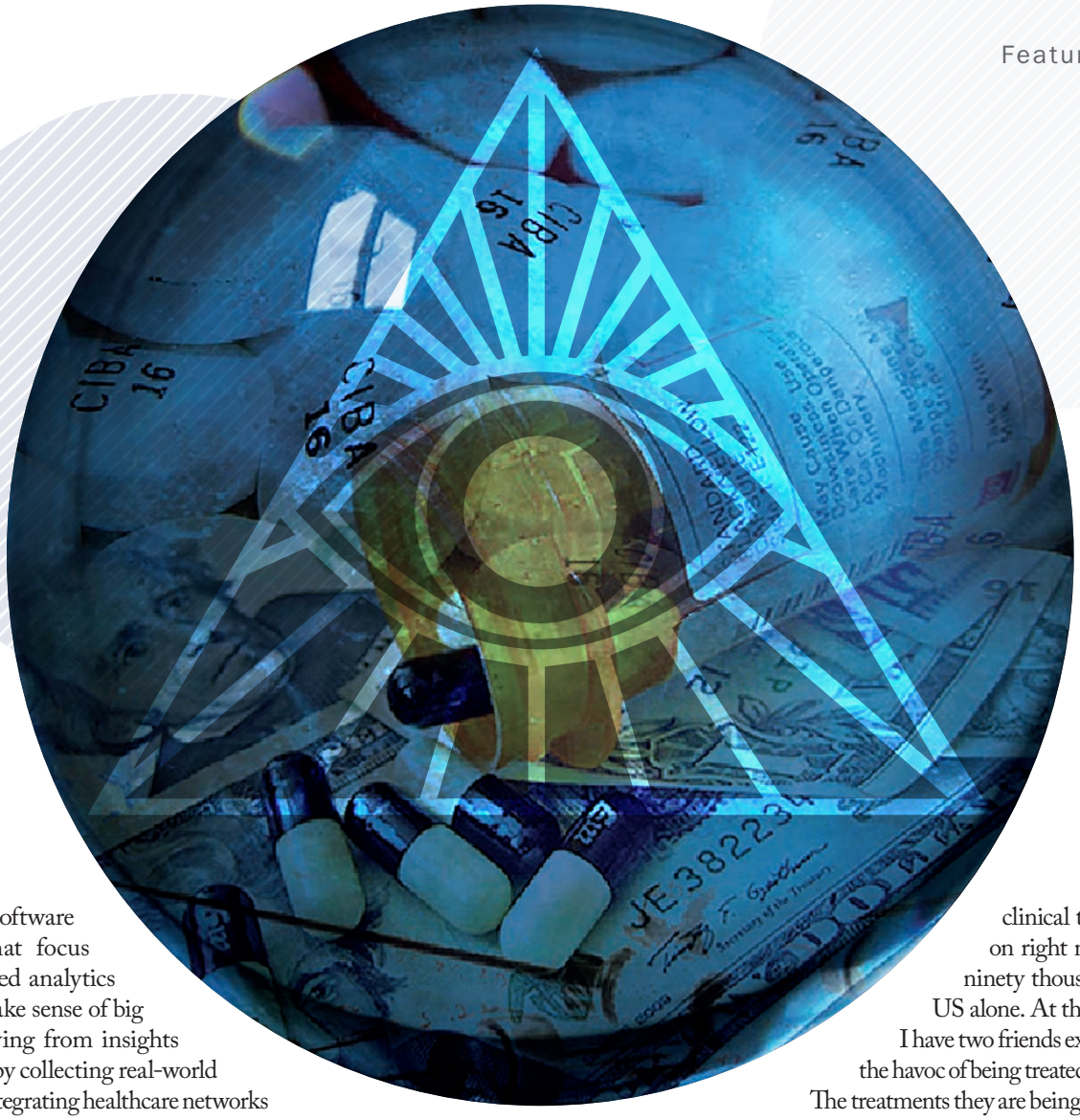
What other 2016 events will impact the industry's future?

MT: President Trump – the exact nature of that impact remains to be seen...

CM: I agree – the overall change in the political environment across many countries will have an effect on the pharma industry, but perhaps it will be positive for patients. For example, the current patient-care system in the US is run by insurance companies and pharmacy benefit managers. The many lines of the Affordable Care Act took a great deal of power from the patient and doctor and gave it to insurance companies – but most patients didn't find out about this until something overwhelming happened to their health. The contracts that go on between drug manufacturers, insurance companies and pharmacies are blocking costs savings. Any decentralization of the insurance system will affect the overall pricing of drug products and open up better and further competition.

JT: I've noted a dampened enthusiasm for investment in the biopharma sector. The emphasis on orphan and ultra-orphan indications, although understandable in the current funding and regulatory climate, has slowed progress on more ambitious disease targets, which could have a detrimental effect on the industry in the long run.

EM: Political events have certainly drawn much attention in the industry, but we shouldn't let them overshadow other trends. Personally, I think it's been very interesting to watch investments increasing in health technology companies; for example, new



oncology software players that focus on advanced analytics tools to make sense of big data. Moving from insights to impact by collecting real-world data and integrating healthcare networks for patient benefit could have a big impact on the industry.

What are you predictions for 2017?

MT: Repatriation of US company profits will fuel deal making, especially M&As. I expect to see many acquisitions in hot areas, such as oncology. However, the unpredictable nature of global markets will continue to surprise us. More specifically, because the biopharma industry is heavily reliant on the US market (its biggest profit pool), any move by Donald Trump and his team will be closely watched – and could lead to strong share price reactions in both directions.

In terms of research, what I like to call "New Biology" (complex cell and gene therapies; immuno-oncology; biomarker-driven stratification of patients to focus on specific disease sub-settings; convergence of big data and drug discovery; and other technological advances) will continue to create lots of data – both positive and negative – which will ultimately have the potential to transform biopharma innovation.

CM: I think that 2017 will be a year of hope. There are many clinical trials going on right now – over ninety thousand in the US alone. At the moment, I have two friends experiencing the havoc of being treated for cancer. The treatments they are being offered are difficult, but the prognosis is good. Not very long ago, either of their diagnoses would have been nothing short of a death sentence. With so much time and money being invested in new clinical trials, new medicines certainly lie on the horizon.

JT: I'm hopeful that early stage research funding will improve, as well as funding for early-stage companies. There is a lot of exciting research out there at the moment. In 2017, CRISPR technology will likely be one of the most promising developments in disease control and treatment. I'm also positive about a potential medication that finally proves to be effective for the treatment of Alzheimer's disease. On the cancer front, 2017 will see an expansion of checkpoint inhibitors into different clinical settings, as well as more research as to how cancer cells modify or alter their metabolism to promote growth.

EM: I think we may see approval of the first CAR-T – there are a number companies hoping for the nod from the FDA, including Kite Pharma and Novartis. Meanwhile, CRISPR launched preliminary human trials in China in 2016 and are hoping to start in the US in 2017. In the diagnostic arena, personalized healthcare will be taken to the next level for cancer

Regulatory Review

With Siu Ping Lam, Director, Licensing Division, UK Medicines and Healthcare products Regulatory Agency (MHRA).

Personally, I think 2016 has been a very exciting and busy year. A great number of new medicinal products have been authorized and the pharmaceutical industry is predicting that more new active substances are coming to fruition in 2017 and beyond. MHRA saw an increase in the authorization of medicinal products via the UK National route in 2016 in addition to the larger number of applications submitted via the usual Decentralized (DC) and Mutual Recognition (MR) procedures, which is interesting because it may suggest that the UK pharmaceutical market is becoming more attractive.

In particular, 2016 was a significant year for enabling earlier patient access to innovative medicines in areas of high unmet medical need. Within MHRA, the UK Early Access to Medicines scheme (EAMS) has now designated 24 products as "Promising Innovative Medicines". Within the EU, an initiative to enable accelerated approval and early access to medicines was introduced by the EMA in 2016 – the Priority Medicines (PRIME) scheme. The scheme is based on enhanced regulatory interaction and early dialogue with developers of promising medicines. MHRA contributed significantly to the development of PRIME.

2016 success stories at the MHRA

- In 2016, the MHRA's regulatory and scientific advice service provided a record number of 411 meetings, with our experts providing advice ranging from regulatory requirements to quality product development to non-clinical testing and clinical trial designs.
- The MHRA Innovation Office (IO) received 131 submissions. The IO was established to provide advice to help particular innovators, individual developers, academia and small and medium enterprises (SME) with regulatory processes and requirements for product development. Over 60 percent of queries were received from academic institutions and SMEs. A large number of queries related to innovative products or interesting concepts at the early development stage.
- The number of first-in-human clinical trials carried out in the UK is increasing. In 2016, MHRA assessed 58 first-in-human trials and 17 trials involving advanced therapy medicinal products (ATMPs). Our assessors have also taken a leading role in the update of the EMA 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' currently out for consultation.

2017 Resolutions

As a regulator, I see one of the priorities for MHRA in 2017 being to actively participate in process development and work collaboratively with stakeholders in the health system to implement the final government recommendations in response to the recently published report in the UK on Accelerated Access Review. Accelerated Access Review should enable patients to have earlier access to and benefit from innovative medicines, medical technologies, diagnostics and digital products for clinical need as the efficiency in the system – from product development to adoption – is further enhanced.

MHRA will continue to play a full and active role in European regulatory procedures in 2017. We will continue to contribute significantly in both the centralized and decentralized regulatory procedures, including new rapporteur and reference member state appointments, and to maintain the program for implementing the clinical trial regulation.

patients with companies like Foundation Medicine, established to focus on analysis and diagnostics. Companies that develop and commercialize genomic analysis/diagnostics for a variety of cancers will start playing a bigger role in physician decision support and more personalized treatments.

What should the industry prioritize in 2017?

MT: We need to continue to build truly collaborative models for R&D, enabling early partnering between large pharma, academia and biotech that bring out the best of each. We also need to develop better pricing models. Despite the sophistication of modern biopharma, pricing models sometimes still feel archaic. Finally, the industry needs to be better at explaining the value of innovation to prevent the public from viewing the industry as an enemy that only wants to maximize profits – in this regard, we need to remember that actions speak louder than words.

"WE NEED TO PUSH PATIENT CENTRICITY BEYOND JUST BEING A BUZZWORD" - EVA MCLELLAN

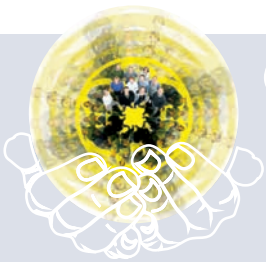
CM: The industry needs to avoid the "status quo". Pharma must tightly control the purity, quality and consistency of products of course, but sometimes the focus on this is so tight that innovation is stalled. Pharma and medical companies must take the time to innovate and adapt their products and services with emerging technologies. How can a new product be tied in with mobile technology? What can we do with drones? What can we do with robotics? What can we do with 3D printing? Can nanotechnology make an existing product more effective? What can we do to make cannabis-based active compounds available as an approved medical treatment? What dosing technologies can be used to make it easier for patients to comply with their treatment protocol?

JT: I agree with Markus – we need to better educate the public about the great benefit and overall value of medicines. For example, there have been plenty of news stories about the high price of Sovaldi for treating Hepatitis C, but what becomes lost in the discussion about price is the fact that Sovaldi has very high cure rates and a short dosing period for an otherwise intractable disease. I'd also like to see the industry renew some of its anti-bacterial research programs. I can imagine an industry-academic-government cooperative program to tackle the increasing issue of drug-resistant microorganisms.

EM: We need to push "patient centricity" beyond just being a buzzword – we need to turn it into an authentic reality. It begins by truly understanding patients' needs, fears, wishes for themselves and their families, and the hurdles that complicate their journey. Patients are our most important stakeholder, and the companies that succeed in truly engaging their diverse and increasingly influential voices will succeed both ethically and commercially. The effort cannot be a project, initiative or priority du jour – we need to rethink who we are as an industry and truly put ourselves in the service of patients as opposed to regulators and payers. It won't happen with "business as usual"; it will take relentless commitment, unprecedented partnership and sacrifice by all stakeholders. But if we begin 2017 with a genuine priority on patients, then transformation awaits.

Siu Ping Lam's Areas to Watch

- Growth in biosimilar products is expected as data exclusivity periods expire for big biologics.
- Immunotherapy is advancing rapidly. Of the 10 medicines in the MHRA's Early Access to Medicines scheme, 9 were for cancer treatments in 2016.
- Significant research activities in dementia are gathering pace.
- Gene, cell and tissue therapies are maturing and gathering momentum. We should gradually see some of these therapies emerging from clinical trials to market.
- There is increasing clinical trial activity for the use of chimeric antigen receptor T cells (CAR-T) in oncology, which involves engineering T cells to recognize and attack tumors.
- Innovative medicines are being developed using gene editing techniques such as CRISPR and TALENS. One exciting development in this area is the development of a CAR-T cell therapy made from donor cells, offering the potential for future frozen, "off-the-shelf" T-cell based medicinal products.
- With more precision medicines being developed, we see companion diagnostics being a significant treatment tool. Recently authorized anticancer immunotherapies use companion diagnostics to detect specific genetic markers and thus select target patients for drug treatment for better outcome. In this regard, the imminent changes in the European Commission's In Vitro Diagnostic Medical Devices Regulation will be very relevant in the future.
- New approaches to clinical trial designs are being adopted, particularly when cost, time and patient population are the limiting factors. We expect to see more clinical trial designs that make use of real world data, comparing the results of a cohort of patients taking the standard-of-care medicine as usual in a real world setting with those taking the drug on test.


Top Articles of 2016

What was hot on The Medicine Maker website during 2016? These were the most-read articles on www.themedicinemaker.com:

The Beginning of the End of Quality by Design

By Jasmine (May 2016)

Where did Quality by Design come from? Where will it lead to in pharma? And will there be a day when its principles are so firmly entrenched that the concept no longer exists?

http://bit.ly/27QT4Iz

Bluff or Serious Biosimilar Bet

By Eva McLellan and Martyn Smith (October 2016)

To understand who is most likely to command the biosimilars game, McLellan and Smith examine the companies at the table, peak at their cards and imagine how they might play.

http://bit.ly/2fRkwBY

The Great British Debate

By James Strachan (May 2016)

Before the surprise outcome of the UK's referendum on its EU membership in June, The Medicine Maker's Associate Editor asked what Brexit might mean for the global pharma industry.

http://bit.ly/1Rcrp8I

A Tale of Irish Biopharma

By Barry Heavey (June 2016)

Biopharma in Ireland is booming today, but what are the origins of this success? And what further investment is IDA Ireland planning for the future?

http://bit.ly/2aIQGfi

The Bright Star of Open Innovation

By Niclas Nilsson (March 2016)

LEO Pharma tells the story behind its Open Innovation platform, which launched in 2015. This platform was also the winner of The Medicine Maker 2015 Innovation Awards.

http://bit.ly/1pHh4M1

Building a QbD Masterpiece with Six Sigma

By Jasmine (August 2016)

Many people struggle with Quality by Design and a common obstacle is getting stuck at Five Sigma. For some, Five Sigma is good enough, but there are a number of ways to finally reach Six Sigma.

http://bit.ly/2fRk7j8

Beyond Keeping Up Appearances

By Charlotte Miller (April 2016)

The perfect drug and the right packaging to protect it – all is well until the medication reaches the patient, who then stores the tablets inappropriately. Can film coatings help better protect medicines?

http://bit.ly/2iAVvtL

The Great American Debate

By James Strachan (September 2016)

Once again our Associate Editor delved into politics – this time looking at what the potential outcome of the US presidential elections might mean for the pharma industry.

http://bit.ly/2eiyB8i

The Cautious Comeback of Oral Peptides

By David J Brayden (September 2016)

After the clinical failure of oral peptide formulations in the 1990s, pharma took a step back, but today select oral peptides are yielding positive data in advanced clinical trials.

http://bit.ly/2jzi46n

Pharma Manufacturing? There's an App for That

By George Mashini (June 2016)

Mobile technology and apps have become a staple of the pharma industry in terms of disseminating information to patients, but much less is known about their impact on manufacturing.

http://bit.ly/2h9IKGC

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2016 Winner
Waseem Asghar

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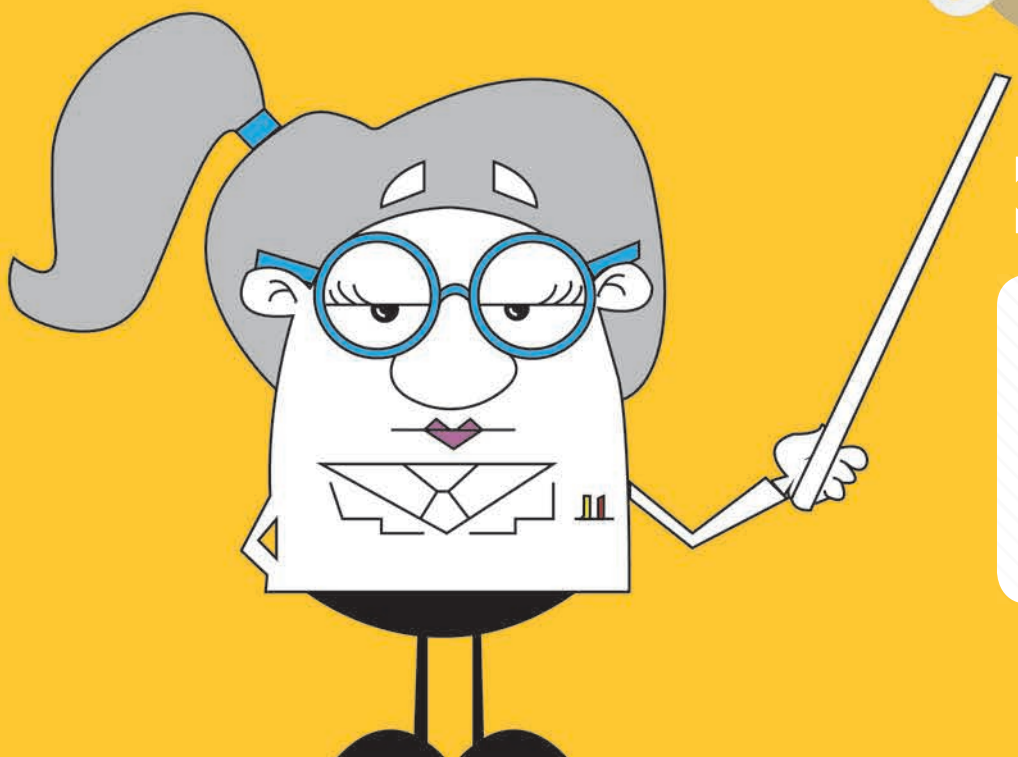

The Bioprocess Model Maker

It's not unusual for companies to struggle with the optimization of bioprocess development. Modeling can certainly help – but what separates a good model from a bad model?

Industry is waking up to the fact that modeling can reduce time and costs in bioprocess development, while also helping to meet Quality by Design (QbD) initiatives. In recent years, data-driven models, in particular, are becoming a popular choice, but developing such models is not straightforward. It is crucial to remember that a model's success hinges on the data used to create it. Jarka Glassey, Professor of Chemical Engineering Education at Newcastle University, UK, tells us more.

Why is modeling so important?

A significant problem in the biopharma industry is that new drugs are expensive. I understand why drugs must be sold at such high prices, but at the same time feel there must be something we can do to change this. Bioprocess modeling, optimization and monitoring control has been a focus of research throughout my career. It's a great field to work in because it can potentially accelerate the development of new medicines, as well as making them more effective and less costly – and therefore more accessible to society at large. Bioprocess modeling is all about using data obtained from the process to organize and improve the process – and it's significantly faster and more efficient than just relying on traditional (and somewhat limited) experimental work data analysis.

Modeling is not something new. Even back in the days of my PhD, artificial neural networks were very

fashionable and there was interest in using simulations to predict process behavior under various conditions to help understand and optimize the process early on. By the time you start producing at large scale, the aim is to have consistent, high productivity – an obvious advantage. Over the years, in collaboration with a number of pharma companies, we have shown that a better understanding of the bioprocess also allows biologists to be much more effective at developing new biopharmaceuticals, as well as better bioprocessing methods to produce them.

QbD and Process Analytical Technology (PAT) initiatives have really wetted pharma's appetite for modeling and statistical approaches, which are now more frequently used in industry than when I was doing my PhD. Principal component analysis, for example, is very commonplace – almost everyone in the industry has heard of it, even if they don't know exactly what it is. But now that the industry is more aware of the power of modeling, there is the potential to take it further.

How are bioprocesses currently monitored?

I've co-written a number of review articles that examine the current state of modeling (1,2). The last few decades have seen incredible advances in analytical techniques, coupled with miniaturization. In particular, there has been a huge drive to develop new, noninvasive sensors, such as spectroscopic sensors or other fingerprinting techniques. Many of these new sensors enable multiple reagents or multiple intermediates to be measured in one go. Rather than having dedicated sensors for every single species, it is now possible to make some estimations about the state of the process as a whole, leading to greater process understanding. For example, we've published an article that links processing conditions upstream during fermentation to the glycosylation pattern of monoclonal antibodies (3).

Current methods have their limitations, however. Biopharma manufacture is complex and even a small change can have a significant impact on the end product. In an ideal world, we would be able to monitor changes in real-time and have the ability to adjust the process in response. Although some of today's sensing technology delivers rapid data, the analysis of that data can be an involved process, meaning that actionable information comes too late.

"Better understanding of the bioprocess also allows biologists to be much more effective at developing new biopharmaceuticals."

If we could measure not just quantity, but also the quality of a product at each step of the bioprocess, we could begin to look at how to modify process conditions to achieve desired quality attributes, which is exactly what the FDA wants for QbD. To do this, we need to be able to measure in-line – and in small concentrations compared with all the other components that may be present in the biopharma broth. It is a significant challenge – even more so when we consider doing it cost effectively.

From my point of view, we either need remote sensing technology – and to this end we are actually working on disposable, printed sensors that can be used wherever needed (4) – or physical sensors that give immediate and reliable answers about product quality. We are not at this stage yet, but the rate of progress in the field of modeling and monitoring is accelerating. In five years' time, things may be very different.

What different types of models are available?

Today, different sensors reveal different information about a process and provide many data points, but converting this to actionable knowledge and understanding is always going to be a challenge. Traditional modeling approaches tend to use mathematical equations based on fundamental principles to form results – and the model is gradually improved through testing, which takes time and work. An alternative to modeling is a data-driven model, which uses existing process data. My work combines both approaches in a hybrid model – using fundamental principles, as well as information collected from various sensors. A hybrid model has the ability to exploit a broader knowledge base (5).

What are the main challenges of working with bioprocessing models?

I would like to draw attention to one particular issue: many companies are jumping on the data-driven model bandwagon without fully understanding how the models work. It's true that modeling approaches are becoming easier to use – some models operate with push-button ease, with the computer doing all the work. And though we want models to be accessible, there is a danger that users are unable to question the validity of the model – especially, if the results correlate with what the user was expecting. When lecturing my students

on data-based modeling techniques, I often give examples of where things go wrong. I've seen many instances where models have been developed with limited datasets – and where the queries being asked force the model to extrapolate beyond the range it was designed for.

Biologists who carry out experiments and understand the biology behind them can often tell by looking at a sensor reading if something is potentially wrong. Increasingly in bioprocessing today, sensors employ spectroscopy or other techniques that produce data that are very difficult for the human brain to interpret; such data therefore enter a model, which makes sense – but we can't expect everyone to be experts in data modeling techniques. Take my example of principal component analysis; it's a very common term in the industry, but even if you've seen its power in a particular context, you may not know exactly what it is or how it works. And why should you? If you are a specialist in bioprocessing, with the task of improving a particular process, modeling is just another tool – and learning everything there is to know about all the tools we may use is unrealistic for most.

Getting the balance right is a big challenge for the modeling community, but I would like to see models becoming more robust and easier to use. The more people automatically turn to modeling, the faster we can build additional interest in the field and advance it.

On the other side of the fence, there is a danger that experts in model development may not know enough about bioprocessing to understand the best data to introduce into the model – perhaps they will choose specific

"Drawing on models in the early days of a new company can influence the entire approach to development."

variables rather than derived variables, for example (which a biologist will often use naturally). Such a decision drastically limits the potential of the model – and I've seen many models written off without being given a proper chance. Data-based modeling techniques are only as good as the data used to develop the model. And one bad experience with a model can put a company off using models ever again...

How can the industry capitalize on the potential of bioprocessing models?

The answer is obvious: we need modeling experts and bioprocessing experts to talk, which is why my PhD students in modeling always have a joint industrial supervisor. My own preference is always to work with industry because it is rewarding to see the impact – and you tend to see verification of your work very quickly in real-life process conditions.

I have always been fortunate to work with people in industry who are very forward-looking and have seen the benefits and value of modeling. But this isn't necessarily the industry standard – and that needs to change. At Newcastle University, we've been making sure that our graduates, whether engineers or biologists, are aware of the power of modeling. It's an important first step, because they will take their knowledge wherever they go.

What is the best way to get started with bioprocess modeling?

Many large biopharma companies already use models – and have the resources to create specific units and departments to invest in the approach. In some instances, they may also be fortunate enough to have well-established academic collaborations. Smaller companies (and especially start ups), on the other hand, may not even have considered modeling as a valuable tool for the optimization of bioprocesses – and that means they are missing an opportunity to gain a competitive edge. Perhaps even more importantly, drawing on models in the early days of a new company can influence the entire approach to development.

How do you get started? Well, you could turn to a specialist company that performs multivariate data analysis or offers partial sequence models based on your data – you simply pay for the results.

"Many large biopharma companies already use models – and have the resources to create specific units and departments to invest in the approach."

You could also invest in a proprietary model, but fledgling companies tend not to have a solid understanding of their own process, let alone enough knowledge to explain those processes for the purpose of model development.

Working with academia can be another effective option – but expect much longer timelines; a PhD student usually needs three years to complete a PhD, whereas a business may only have six months to make a crucial decision on whether to go ahead with a project or not. That said, taking the academic route does develop solid process understanding along the way. Importantly, academics have the freedom to use whatever tools are most appropriate; many companies that already have a specific approach to modeling tend to try to shoehorn everything into that current modeling approach, whereas academia tends to look more broadly at what will best suit each individual project. Overall, I think it's really important for industry and academia to work together more. Academia can come up with fantastic ideas, but they are not always feasible in the real world because of cost. Academia can learn realism by collaborating with industry, whereas industry benefits from academia's freedom of exploration, which often results in breakthrough ideas as opposed to incremental improvements.

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Is Flexibility the Way Forward for Female Leaders?

Men continue to dominate upper management positions, but businesses also need the talent and diversity women can bring to drive bottom line results. With a focus on flexibility, things could change for the better.

By James Strachan, Rosalie Harrison and June Nilsson

The debate surrounding "women in the workplace" has changed in recent years. The case for more female hires and more women in leadership positions is now rarely made on moral and fairness grounds. Instead, the argument is a business one, built upon the increasing acknowledgement that greater leadership diversity is good for the bottom-line. The logic is fairly simple; women are not a minority. They represent more than 50 percent of the human population, and they are as educated, ambitious and able as similarly situated men. As such, if a company has an all-male leadership team then the likelihood is that it has not attracted or retained the top available talent.

The topic of women in the workplace was tackled by Borderless during a presentation at the CPhI Women in Leadership forum in Barcelona, Spain (1). Borderless is a search and management consulting firm that specializes in bringing talented, globally-minded leaders to client companies in the life sciences and chemical sectors. In the life sciences industry alone, women actually represent 60 percent of new hires, but begin to be far outnumbered by men as early as the senior manager level positons and above. In fact, the higher up the ladder you look, the greater the discrepancy – and when you see statistics showing how women drift off as you move up the career ladder, you can't help but think of all that wasted talent.

Tackling this problem is a business imperative. We should all be asking ourselves, "What could this wasted talent accomplish if it could be retained?" Diversity brings different perspectives to the workplace, which become increasingly important at higher leadership levels. By introducing new and different ways of thinking to management and board level positions, companies can become more innovative. As well as helping clients attract and retain diversity minded leaders (both men and women), Borderless also advocates that it is time for corporate cultures to embrace a new concept of career flexibility for workers – and for professionals to begin expecting and asking for it.

The business case for flexibility

The world of business – especially in the life sciences industries – is undergoing a number of dramatic changes that actually support a more flexible approach to careers and career progression. Such an approach to careers has already been embraced by the tech industries, which are increasingly moving into the healthcare sector and intensifying the competition for the available talent. As a result, non-linear careers and careers in phases – which have often been needed for female professionals with family responsibilities (an estimated 80 percent of women) – are becoming more commonplace for all workers, particularly in light of the fact that both men and women in the millennial, post-millennial and Gen-X generations tend to favor flexibility over pay as they prioritize work with other life ambitions. These generations tend to expect and seek work environments with greater diversity and room for individual contribution and expression. When employers accept the idea that careers can progress in phases – rather than in straight lines – the pipeline for upper management positions can evolve quite differently – and is often favorable to the inclusion of more female professionals. This move away from traditional, vertical career paths, however, means that more industries will be competing for talent – pharma needs to make itself attractive with flexible environments if it wants to attract and retain the best workers.

Shifts in stakeholder demographics are another reason for pharma to support efforts to increase flexibility. For example, one particular challenge for the life sciences industry is the growing importance of patient centricity and caregiving, which is leading to a change in the kinds of skills and insights that are required for key business decisions and strategy. It is well-known that women are often at the center of patient-centric decisions in the family, such as choosing healthcare providers for their families and making healthcare decisions. Women, therefore, as well placed to offer valuable insight and perspectives in patient-related decisions.

"What could this wasted talent accomplish if it was retained?"

The recent appointment of Emma Walmsley as CEO of GlaxoSmithKline is a recognition of the trend towards patient centricity. Ms. Wamsley has no scientific drug development skills and was not hired because she has the next blockbuster in hand, but because of her strong marketing background in a consumer-focused business environment. She has spent much of her career in an environment at L'Oreal, where the customer is the center focus. Pharma companies need employees who can understand and work within this customer-focused framework.

Asking for what you need

Traditional work environments and lockstep careers have never been the friend of the female professional – and this will not change in the near future. With an aging demographic and longer life expectancies, care for children and aging family members is a growing concern for all workers, of course, but it remains a particular challenge for women, who continue to shoulder the primary responsibility for such care-driven activities. While hard work, talent and ambition remain the keys to career success, it may not be

Getting to Know the Authors

What is your background?

Rosalie: I started out as a registered pharmacist in the US working in a large clinical teaching hospital. Then I went into the pharma industry where I worked on transdermal drug delivery studies, which were fascinating, but the loneliness of research just wasn't a fit for me. I moved into pharmaceutical sales for some time and then went back to school to get my law degree.

June: I was born in Sweden and I actually started reading South East Asian Studies at university, but then I decided that I wanted to study abroad. I went to Germany and ended up doing a master's in clinical science and economics. My big passion at university was reproductive health, but from the perspective of control rather than a science perspective. With that in mind, I went to India to conduct research.

What led you to borderless?

Rosalie: After getting my law degree, I went into big international law firms and made my way up to partnership. I worked on labor employment law, where I developed a passion for the employment relationship. I also did a lot of work with discrimination and sexual harassment – and I became very involved in issues that affect women in the workplace. When my husband had the opportunity to take a job in Germany, I left the law firm. Our children were five and eight at the time, so I threw myself into being a mother and in learning to live internationally. Once we moved to Brussels, my children were getting older so I decided it was time to go back to work – and I ended up at Borderless. I came to Borderless with 20+ years of experience and I think I am a good example of someone who has engaged in her career in phases.

June: After working for the German development agency in India, I had the opportunity to join a start-up company in the tech sphere as the human resources (HR) manager. I had never done HR before, but I took the plunge and it was a great learning experience – I built the processes from inside out and was responsible for all the recruitment. I met my husband while in India and his company offered him an opportunity in Brussels, which is where we ended up, and where I found Borderless.

What made Borderless a good fit?

Rosalie: The Borderless role combined my life science, employment and expat background. I did a lot of litigation when I was a lawyer, so I was very much working at the death of the employer/employee relationship. Now I'm at the birth of the relationship when people are excited to get together. Most of all, I'm really motivated to help people meet their potential.

June: Borderless was great in that it brought together lots of the elements I've learned over my career – particularly my international background and my HR experience. I enjoy getting to know the client and finding out exactly what their needs are (they usually don't know!), as well as exploring where people want to go next, where their passions lie, and how they might fit into an organization. Helping that process is extremely satisfying.

WOMEN IN THE US WORKPLACE

Women earn more degrees than men

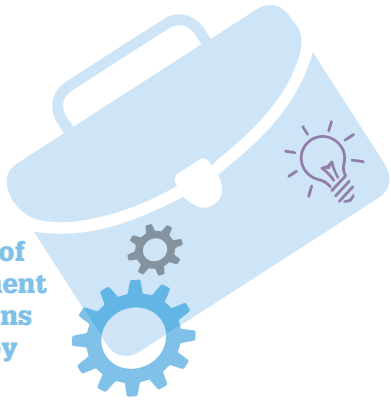
For the class **2013-2014**, women earned more than half of bachelor's degrees(**57.1%**), master's degrees (**59.9%**), and doctorate degrees (**51.8%**).

Women comprise nearly half the labor force

In 2015, there were **73,510,000** women aged 16 and over in the labor force, representing **46.8%** of the total labor force.

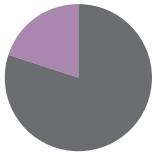
The majority of women are either working or looking for work. **56.7%** of women participate in the labor force, compared to **69.1%** of men.

More than half of management occupations are held by women

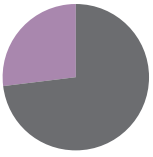


In 2015, women held **51.5%** of all management, professional, and related occupations and **43.6%** of the subcategory management, business, and financial operations occupations.

The overwhelming majority of new directorships continue to go to men



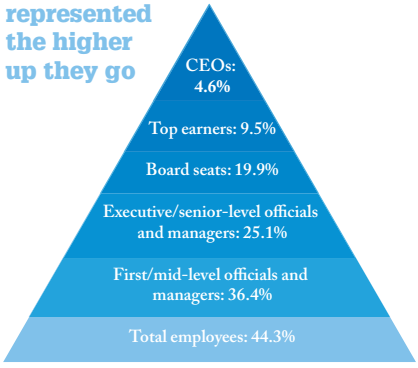
Men held 80.1% of S&P 500 board seats, while women held 19.9%.

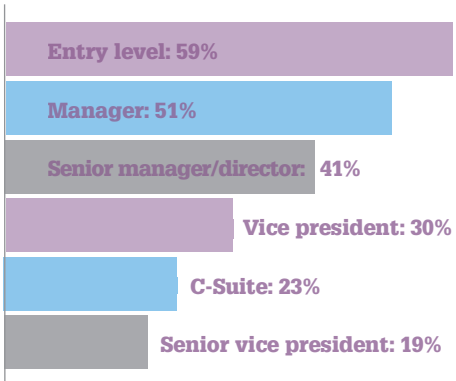


Men held 73.1% of S&P 500 new directorships, while women held 26.9%.

2.8% of S&P 500 companies had zero women directors, **24.6%** had one woman, and only **14.2%** of companies had **30%** or more women on their boards.

In S&P 500 companies, women are less represented the higher up they go



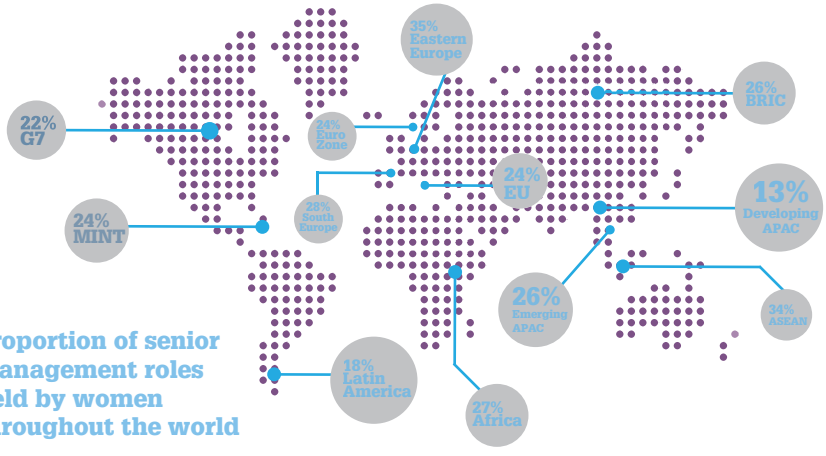


Women in healthcare and pharmaceuticals

37%

Over 37% of talent acquisition leaders believe that diversity will be the number one trend that will define the future of hiring.

Diversity is becoming one of the main priorities for companies worldwide



Proportion of senior management roles held by women throughout the world

Information sourced from:

Catalyst, "Women in the workforce: United States", (2016). Available at: http://bit.ly/2hXGupW. Last accessed January 6, 2017.

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enough in an environment that also lacks flexibility to enable professionals to meet other demands in their lives. Female professionals should seek out and support environments where it is acceptable to ask if there is a different, more efficient way they can work that does not compromise performance standards.

During the CPhI conference, Borderless provided a few real-life examples to inspire female professionals to seek the flexibility they need. One way to find flexibility is to establish it early in the working relationship. When looking for a new opportunity within your organization, make sure that they know you're the right person for the role. How? You must understand your own value and, crucially, know how to put it into context and communicate it. Think creatively about what you need to be successful in the role and ask for it – the key is to make a compelling business case. One example from Borderless related to a managing director of a pharmaceutical company. She was asked to take on a new role at a time in her life when her children were still very young. She was very keen on the role and her employer was keen for her to take it up, but she also needed and wanted time to dedicate to her children. She boldly asked for a work schedule that would enable her to work from home on Wednesdays. Although she faced some initial skepticism, she argued passionately for a period of six months to prove that she could make it work. Her employer obliged and, sure enough, she was successful. Put simply, it's a case of knowing you can do a job well and asking for what you need. At the same time, employers need to trust the judgment of valued employees.

In a second example, Borderless approached a female professional for a leadership role at a pharma company. It was a dream job and fit with the candidate's expertise, but she would not even consider applying for the position because the travel requirements did not fit with her family responsibilities. Borderless encouraged this female professional not to get discouraged about the travel, but to think creatively and flexibly about how she could work in a different way. When given permission to think flexibly, this candidate developed a robust system for communicating on a regular basis remotely utilizing the latest technology available, which reduced travel costs and promoting efficiency for her entire team. While some travel was still required, this professional – by asking for flexibility - proved that it was possible to execute the role successfully completely differently from her more traditional male predecessor.

In short, build your case, think creatively, expect flexibility and don't be afraid to ask for what you need to do the job, keeping in mind, of course, that performance standards must be maintained.

"Employers need to trust the judgment of valued employees."

The way forward

The above examples demonstrate that creativity, when coupled with flexibility, can lead to mutually beneficial arrangements. Organizations need to create an environment that attracts the very best talent – and that means meeting the needs of an increasing number of female professionals and new-generation workers who value flexibility over pay and see diversity as a fact of life. As a company positioning itself for success and competitive advantage, you should be strategically focused on your organization's flexibility. Do you have open doors for women (and men) who have taken a career break? Are you willing to take a chance on someone who wants to work remotely to reduce travel? Successful organizations tend to be the ones that differentiate themselves in terms of flexibility. Your hiring strategy shouldn't be a box ticking exercise with the goal of filling an arbitrary quota. Instead, by combining a strong emphasis on diversity of opinion, experience and mind-set with a flexible process that gives people the chance to prove they can perform, you can maximize your chances of attracting the very best talent and creating a strong and dedicated team.

Rosalie Harrison and June Nilsson are both consultants with Borderless, Brussels, Belgium.

Walking the Entrepreneur's Path

It's not easy finding your way "from a garage to a palace." The journey requires creativity, persistence, humanity – and a little luck.

By Rafaat Rahmani

I started Lifescience Dynamics – a decision-support firm – in my garage in 2004 with just £7500 in the bank. I had no investors and no clients. I was often concerned I wouldn't make it. Today, I am pleased and proud to say that the company works on a global scale and in 2016 we won a Queen's Award for Enterprise in the UK for the category of International Trade.

My early career wasn't focused on pharma. In fact, one of my first jobs was selling the Encyclopedia Britannica door-to-door. Looking back, it is incredible just how frequently I draw on the skills I learned in those early days. Indeed, salesmanship is an invaluable skill for most entrepreneurs; you need to sell your concept, your product, your services and yourself every day. After that, I did some odd jobs during my undergraduate studies in the US, before working as a Marketing Manager for McDonalds and Pepsi. This helped me to develop skills in branding and marketing that were pivotal in the early days of the company. For example, shortly after starting Lifescience Dynamics, I landed a contract with a large pharmaceutical firm – unbeknownst to them I was working alone in my tiny garage office. Marketing can be a powerful tool, helping you to project the right image to prospective clients.

After Pepsi, I spent some time as a general manager for a company in Dubai before moving back to the UK to study for an MBA at Manchester Business School. Despite completing several projects relating to pharmaceuticals and healthcare during the course, I wasn't actually interested in pharma at that time. I wanted to go into consumer goods, but big pharma companies often visited the campus to recruit and I decided to attend an interview anyway; more for practice than anything else. I must have done or said something right, because Eli Lilly offered me a job, much to my surprise. I had no pharmaceutical background and I hadn't studied life sciences. In hindsight, it was one of those fortunate, life-changing events that holds a significance you can't possibly be aware of at the time.

Eli Lilly was a fantastic company to work for. They put me in a development program used to train future country managers. Every six to eight months, I would be in a new role, in a different country. I did stints in market research, competitive intelligence, price reimbursement and brand management. Again, I didn't appreciate the value of what I was doing until years later. It really helped me to develop a full understanding of the pharma industry from almost every functional area. But I had a young family and the traveling was not ideal, so I started hunting for something new.

I was then introduced the founder of Double Helix, a pharma consulting company, and ended up working with him for six years. After that I was itching to set up my own business.

Know thyself, know thy market

The two Internet-based businesses I started during the late 90s' unfortunately failed. The first, Deal.com, aimed to auction off abandoned clinical trials

and data concepts that other smaller companies might have been interested in. This meant that expensive research carried out by large pharma companies, who did not see the profit in continuing with the study, could still be utilized. This venture failed due to the vast amount of legal matters involved with data transference, which was not my specialty. I didn't have a strong legal background it became evident that this was not the best practice for me.

ICare, my second venture, focused on homecare that increased patient engagement, product familiarization and pharmaceutical drug compliance using a digital platform. In short, ICare was a customer service arm of the pharma company, providing their drug users with the aftercare support that they might not necessarily receive from their doctors. This failed due to the lack of financial support. I required at least 2 million to develop the concept fully, and with this being a relatively new idea for its time, it was difficult to launch. Consequently, Atlantis Healthcare have now successfully developed this concept and are the leading providers of aftercare support; proving that the model itself was effective and there was indeed a gap in the market for such a business if you had the finances.

With these ventures behind me I asked myself, "What do I know?" The answer was consulting. During my market research, I found that there were three primary practice areas for consulting: competitive intelligence, market research, and market access, pricing and reimbursement. There weren't, however, any companies doing all three – what we call "decision support." I came up with the idea of offering statistical advice across all three practice areas; to explain where the market was yesterday, where it is today, and where it will be tomorrow. Hence, my third venture, Lifescience Dynamics was born.

Finding a gap in the market and developing a solid business plan is one thing, but turning that into a successful business is another entirely. In the pharma sector, it's common for two to five senior people to set up a fledgling company; often with one or two clients. But when I left Double Helix I had a two-year non-compete clause which tied my hands. I had no clients and with no external financial backing it was a real struggle. I ended up sending emails from my bedroom before investing £800 to convert a quarter of my garage into an office.

"There were three primary practice areas for consulting: competitive intelligence and market research, market access, and pricing and reimbursement."

It was a risk, but the pharma industry is a very risky business. Drugs can take a decade to develop and during that time there's a huge amount of money and time invested; getting things wrong at the outset can have disastrous consequences. Therefore, it's important to position yourself as the solution to a problem that isn't being answered by anyone else. Our solution was to use support statistics as a means of working out what kind of drugs to make, what markets to enter, to understand the clinical endpoint, how to neutralize the competition and how to make the drugs affordable and accessible. Thereby, making us an asset to our clients.

A recipe for success?

I believe there are a several prerequisite personal qualities to be successful as an entrepreneur. The first is a willingness to dream big. From the outset, even when sending emails from my bedroom, I dreamed of being an international company. Today, we work with many of the top 20 pharma companies and have a strong customer base in the US, Europe and Japan. The Queen's Award for Enterprise was partly in recognition of the fact that we have had consistent and durable growth since 2010 – and doubled in size from 2014 to 2015. We attribute this success to the quality and diversity of our employees and the support of our clients who continually offer repeat business.

Another important personal quality is self-discipline. For the first two years, I didn't have any employees and it's easy to put work off when you're only answerable to yourself, so you must be focused. You must also have a positive attitude. You will feel rejected at times, but you have to be able to learn from set-backs and move on. The ability to creatively solve problems is a must, as is the age-old sales tactic of never taking no for an answer.

Another factor is bringing in the right people – and this has probably been the biggest challenge we've faced as a company, particularly when competing on the global stage. Big companies can afford to take on anybody from anywhere. We are looking for the kinds of people who work for big management consulting firms, so there is fierce competition for talent. It was difficult getting people of the right caliber to join a young company that couldn't offer a set-in-stone future development plan.

Despite that, I made the decision to focus on employing people with pure life

Rafaat's Predictions for 2017

I believe that "real-world evidence" will play a big part in the years to come. As a company we're not in that area at the moment, but we can see that adaptive licensing and adaptive reimbursement are going to become increasingly important. Companies will come to value a drug at a certain price, agree to pay that amount now, but in two years' time if the data says something different there will be a renegotiation depending on the effectiveness of the drug.
The other trend is the blurring of traditional pharma companies as other technology companies try to enter the pharmaceutical sector. Pharma companies then leverage the technology to deliver more effective outcomes and positive experiences for the patient. I think we'll see huge changes in the industry during the next five years.

science backgrounds and I really think this has helped me grow the business. I think it's vital in our industry that people have a deep appreciation of the science of diseases at a molecular level. We look for people who have strong life science degrees: Bachelors, Masters and PhDs – and even going back to A-Level (studies done at 16-18 years) they must have studied biology, chemistry and math. Today, 75 percent of our employees have PhDs from top UK universities and almost everyone else is educated to Masters level. Many people told me that I wouldn't be able to find enough people with such criteria, but I always argued that it's important to have high standards. In this business, unless your employees have a solid grounding in the life sciences, they'll struggle to understand the science behind the medicine – and for us that's vital.

The final (and perhaps most important) key to success is fostering the right company culture, which should apply to all businesses. In my mind, people are everything: they are your brand, your assets and your reputation. With this in mind, I set out to build a company that has a heart and soul – a family company with entrepreneurial spirit. So I championed fairness, dignity, and civility. I don't like to run the company as a pure "corporate," so there are no stringent sales or profit targets. We also endeavor to hire people who are genuine and down to earth. My overarching aim is to foster innovation, quality and empathy for the client.

Of course, we've had to overcome hard challenges to get where we are today. Those who've been there know that getting the first client on board is always difficult. A lack of track record and experience is tough to overcome (recent graduates applying for jobs may sympathize here), but that's where persistence and flawless branding and marketing can pay dividends. Cash-flow is also always a problem in the pharma industry because of the notoriously long payment terms – and it was nearly our undoing in the beginning. During the financial crisis, we almost collapsed (and I was actually refused a bank loan). Our answer to hard times? Work harder! We stabilized our cash-flow and grew the business from there. Today, I'm proud to say that we're still a completely independent company – we don't have any investors, I don't have any partners, and I haven't borrowed a single penny from the bank. I will always be grateful to those employees and clients who have been willing to walk with me.

Rafaat Rahmani is the founder of Lifescience Dynamics, UK.

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Business

Economic drivers
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Is the Price Right?

Pharma's business model is increasingly shifting towards expensive specialty medicines, but how much are governments and society willing to pay for these medicines? We need new business model designs and analytics to help measure value.

By George A. Chressanthis

"There are no solutions. There are only trade-offs." Thomas Sowell, Economist and Senior Fellow at the Hoover Institution, Stanford University

The pharma industry is increasingly focusing on complex specialty medicines to treat challenging diseases, but there have been several "flash points" when it comes to the cost of these new therapies. A selection of examples can be seen in the sidebar on page 47 and it is fair to say that drug pricing is a hot-button issue. In Europe, the topic of what drugs should be paid for (1) and how much could be taken up by the European parliament (2) has also triggered a reaction from the European Federation of Pharmaceutical Industries and Association (EFPIA), which has been discussing an outcomes-based reward system (3).

In the US, pharma companies have come under significant pressure at both a state and federal level for the pricing of specific drugs (4). A recent review of pharmaceutical corporate filings and conference call transcripts found that pharmaceutical sales were mainly driven by price increases, which raised political concerns in Congress as well as the threat of price controls, which I discussed in the November issue of The Medicine Maker (5). There are also ramifications for shareholders because this practice is not economically sustainable in the longer run (6). How has the industry reached this critical point?

The trade off

Academic research has chronicled the industry's efforts to address long-standing R&D productivity concerns and how this has influenced a shift in focus to specialty medicines (7, 8). Specialty medicines – many of which are biopharmaceuticals or based on genomic approaches – can help address unmet medical needs and also offer greater price freedom, since there tends to be less competition. Even after patent expirations, the entry and impact of biosimilars is generally seen as more limited given the development costs, as well as the hurdles involved in gaining acceptance from the medical community (9–11). Although branded biologics generate a longer period of revenue after patent expiration compared with small-molecule drugs, there is (as suggested in the opening quote by Thomas Sowell) a trade-off. Specialty medicines cater to smaller patient populations than primary-care driven drugs – about 60 percent of drugs in the specialty medicine category have orphan drug designation (12) or cater to much smaller personalized medicine segments (13) – so the cost per patient treatment needs to be high for companies to amortize a return on increasing R&D risks and costs (14).

Specialty medicines now account for a significant proportion of US drug spending; more than half of the country's drug spending growth in 2015 could be attributed to drugs that had been available for less than two years (15). Similar spending growth can be attributed to specialty medicines in other developed markets too (16). The upshot is that government healthcare budgets are feeling the pressure, which is impacting patient access.

We now have a rapidly growing gap between pharma's efforts to bring new drugs to market, and societal willingness and ability to pay for them. The issue is especially acute with anti-cancer drugs, and has generated much analysis on cost and pricing trends (17, 18). In particular, it can be difficult to decide how to finance drug use for a disease such as metastatic cancer, where life is extended by a limited time. To this end, both American and European oncology societies have developed frameworks to assess the benefits of new cancer treatments relative to their costs; the aim is to help clinicians and patients to make decisions regarding the value of these treatments (19, 20).

Countering the conundrum

How can pharma companies address the pricing challenge? Unfortunately, current academic literature on biopharma marketing offers little insight. Published works tend to emphasize a tactical, non-strategic economic model framework myopically focused on maximizing return on investment across various promotion channels, with the aim of increasing physician prescriptions (21). I believe that the growth in specialty medicines means that we require a completely different commercial model design and accompanying analytics. Consideration for – and demonstration of – value must be infused into pricing analyses, firstly in support of the final decision before launch, but more importantly throughout the entire project/product lifecycle. I've given a non-exhaustive list of suggested company actions for the pricing of specialty medicines pre-launch in the sidebar on page 48. To support these actions, however, pharma companies will need to think very differently about their commercial model design. In addition, traditional pharma sales/promotion response analytics need to give way to new marketing models, which must be informative in nature and deliver scientific evidence using metrics

Pricing pressures – recent examples in the US and UK

A drug for the treatment of cystic fibrosis costs more than $300,000 per patient per year (1).

Combination therapy drugs for the treatment of advanced melanoma costs more than $250,000 per patient for the first full year (2). The UK's cost watchdog, the National Institute for Health and Care Excellence (NICE), rejected one of these drugs for the treatment of non-small cell lung cancer (NSCLC), even after a cost-sharing arrangement proposal, because of a cost of £91,100 per quality-adjusted life year (QALY) (3).

A drug for the treatment of hepatitis C costs $84,000 per patient for a 12-week course of treatment (4). NICE has approved the drug as cost-effective, but global healthcare budgets will be exhausted if the millions of patients who would benefit from the drug went through treatment.

A drug for the treatment of lung cancer costs £51,000 per patient per course of treatment. This price was agreed after two rounds of price cuts and negotiations with the UK's NHS (5).

Another drug for the treatment of NSCLC and pleural mesothelioma was originally priced above £82,000 per QALY, according to NICE (5).

Lastly, another drug for the treatment of cancer was originally priced at £43,000 per QALY, rising to £65,000 and £89,000 for advanced stages, according to NICE (5).

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ultimately tied to improvements in health outcomes, total treatment costs, and cost effectiveness (22, 23).

Commercial activities to support company pricing decisions in a specialty medicine environment can be divided into seven interdependent buckets:

1. *Commercial model design.* The go-to-market approach and model design necessary to achieve all company strategic goals. This approach is dependent on the drug technology of the project/product portfolio that can be successfully developed and tactically executed, while mitigating external threats and positioning the company to take advantage of opportunities (for example, define metrics to determine success and how company resources will be positioned/organized/coordinated to ensure the achievement of stated company goals).
2. *Payer analytics.* Focusing on the parties responsible for reimbursement, whether they be private-managed markets and/or government-based reimbursement plans, as well as analyzing effects from changes in plan design, and their relationship to sales, marketing, and patient outcomes.
3. *Patient analytics.* Analyses generated from real-world evidence and patient-level data on outcomes (for example, drug compliance and adherence, drug costs, treatment costs, health outcomes, cost-effectiveness) resulting from drug utilization.
4. *Sales analytics.* Processes and outcomes related to ensuring optimal sales force investment efficiency and result effectiveness (for example, sales force strategy outcomes, territory alignment, call planning, objective setting, incentive compensation, sales performance metrics, sales reporting).
5. *Marketing analytics*. Processes and outcomes related to ensuring optimal brand performance throughout the entire lifecycle.
6. *Commercial analytics innovation.* Basic research activities designed to generate new management/marketing science methods that

can address future commercial problems faced across the entire project/product lifecycle, including experimentation, collaborations with academic researchers, and other activities to encourage innovation.

7. *Cloud information management*. The focus must be on speed, agility, and scale in association with managing new data sources, elastic infrastructure, data quality & accuracy, and actionable insight in support of activities in all of the preceding commercial analytics buckets.

In a small-molecule drug world, these commercial analytics "buckets" were traditionally seen and conducted as distinct, separate activities. Today – and increasingly in a future likely to be driven

How to price medicines – pre-launch

- Start thinking about pricing and market access early in a product's lifecycle. Pricing should not be an after-thought once clinical work has been completed – it should be infused throughout the entire project.
- Market access and cost considerations should be a deciding factor when choosing which projects to take into further development and clinical trials.
- Clinical trials should be structured so that the demonstration of value can migrate into commercial strategy and operations, which means greater coordination and information sharing between clinical and commercial teams.
- Phase III clinical trials of drug candidates should be measured not only against placebo, but also leading generic and branded drug therapy treatment options (where appropriate). Research-based branded drugs cannot compete against generics on the basis of cost. The only way for a patented, specialty medicine to succeed over a competing older drug is to demonstrate value over cost.
- Payer and individual patient affordability should play a major role in determining economic viability when deciding whether to move forward to phase III.
- The construction of forecast simulations should be done no later than the phase III decision point (and after that it should be continually updated as new information becomes available). Variations in product attributes (relative to the competition), product risk profile, regulatory decision risk, market dynamics (for example, order-of-entry and time delay in the marketplace), managed market formulary acceptance, and individual willingness and ability-to-pay must be accounted for. Sales and marketing activities should be seen primarily as channels to disseminate medical information about product net value attributes to payers, physicians, and patients – not as the principal mechanisms that determine brand success.
- Performance-based pricing will become the norm from payers, which means the HEOR and RWE teams will play a major role in determining a specialty drug price. Managed care plans today are making decisions on formularies that are based on evidence of value. They are also looking to guidelines and the treatment pathways being adopted by providers – which are also driven by evidence of outcomes and value. Effective sales and marketing activities are only possible if the established price point ensures optimal payer formulary acceptance, physician adoption, and patient compliance and adherence.
- Performance-based pricing contracts will require companies to leverage mobile technologies (where appropriate) that protect individual patient information, and allow for self-diagnosing and self-monitoring of patient behaviors to demonstrate product success. As an added benefit, such technologies show patients the continuing progress and value of their drug therapy, which should boost drug adherence, improve health outcomes, and lower cost of care.
- Given the high cost of specialty medicines to patients, companies need to develop cost elasticity analyses on patient out-of-pocket expenses to support the development of patient assistance programs, which will have an impact on the drug net price.

"Consideration for and demonstration of value must be infused into pricing analyses."

by specialty medicines – these analytics are rapidly becoming interdependent activities. Moreover, outcomes from payer and patient analytics will become the principal emphasis and drivers of all commercial decisions. For example, construction of the right commercial model design and the analytics in other areas will all support payer and patient outcomes. Therefore, future applications of commercial analytics will require greater coordinating and linking among all preceding seven buckets. In addition, insights from health economic and outcomes research (HEOR) and real world evidence (RWE) modeling needs to be built into commercial analytics for practical execution to pharmaceutical customers.

In conclusion, specialty medicines represent a wealth of opportunities for pharma companies – rapid developments in science are addressing unmet medical needs and improving care. The challenges of pricing and market access, however, should not be underestimated given that there is increasing resistance to high drug prices. To be successful, pharma companies must think differently about how to prepare these drugs for market launch and beyond – and be prepared to use analytics in new ways to support pricing decisions.

George A. Chressanthis is Principal Scientist at Axtria.

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Leading the Way

Sitting Down With... Dominic Carolan, CEO, National Institute for Bioprocessing Research and Training (NIBRT), Dublin, Ireland.

What drew you to biopharma manufacturing?

I wasn't actually the kind of person who was fascinated by science or the idea of making medicine at a young age. My first job was as a process engineer – but in a large fertilizer complex start-up in Cork, Ireland. It had a huge number of complex processes and equipment – as a fresh graduate engineer I felt like I was in Legoland! After that, I joined a Cork-based European pharma company, which was focused on extracting active ingredients from the ginkgo biloba tree. It became clear to me that I wanted to be involved in starting up and operating large, complex pharma sites.

How did you end up at NIBRT?

It has been a long journey. Along the way, I started up two biopharma production sites for US multinationals, acting as site general manager in both cases. One site was for Mallinckrodt Medical in the 1990s, in Dublin, focused on small-molecule synthesis. The second was a Genzyme biologics operation in Waterford, Ireland, in the early 2000s. I learned that I had a real interest in building successful teams and in 2008, I became Senior Vice President Manufacturing, with responsibility for a number of Genzyme manufacturing sites in Europe and the US.

But in 2014 – after decades in the industry – I decided it was time to do something different, so I set up my own consultancy company. Soon afterwards, I received a phone call about the NIBRT role and was immediately enthused. I'd already spent two years as the chairman of Biopharmachem Ireland, and many more years as a Council member. I understood the needs of industry, both from a training perspective and from a manufacturing and research perspective – the two core tenets of NIBRT. I felt the role was ideally suited to me, and I was delighted when I got the job!

What changes have you seen in the industry over your career?

The big change is the advent of biologics – monoclonal antibody products are well-established, and gene therapy products are on the way. Nevertheless, biologics manufacturing is relatively immature compared with small molecules and there is much we can do to improve bioprocessing. On the small-molecule side, we've seen efficiency improvements from lean techniques and the greater use of automation, although this still lags behind other industries, such as oil and gas.

The dramatic increase in regulatory requirements and inspection visits is another high impact change – large production sites may have multiple day inspections every second week, which is extraordinarily onerous. One reason for this is that, twenty years ago, emerging economy regulatory agencies carried out truncated inspections, but now they are as in-depth as an FDA or EMA inspection. Mutual recognition of inspections is long overdue!

I've also noticed that job roles have become much more specialized and, because of the complexity of the industry, this is leading to a silo mentality. I think that we had better collaboration a few decades ago when there were more generalists.

What are your biggest achievements at NIBRT?

When I took over as CEO around 18 months ago, NIBRT was already well on the way to the success it currently enjoys, but I hope I've helped coalesce the team around our key priorities, and thereby contributed to our recent growth rate (of more than 20 percent). One key success has been the industry demand for our training courses – we had over 4,000 trainees in 2016, many of whom were international. We've also set up successful collaborations with partners such as Bristol Myers Squibb, GE Healthcare and Thermo Fisher Scientific, covering not only training but also manufacturing research. And we've significantly developed a biologics product characterization-focused contract research business based on the bioanalytical expertise of NIBRT's Pauline Rudd and Jonathan Bones.

Why are you so passionate about biopharma training?

There's already a huge demand for trained personnel to meet the industry's current global growth – and this will only increase in the future. This industry is changing rapidly and we need to keep pace by fostering an industry culture of lifelong skills acquisition. Many companies claim to recognize this concept, but we need more to actively support it. Nobody can cram all of the skills and training required for biopharma manufacturing into an undergraduate or a postgraduate degree – the field is far too complex.

Our pilot plant allows trainees to gain hands-on experience with upstream, downstream and finishing technologies without putting product or operations at risk. Back when I was at Genzyme, we had to process batches that were worth €25 million each, which puts tremendous pressure on the operators, who would be almost frozen into inactivity at the thought of the cost of a single mistake! NIBRT helps prevent that situation by allowing operators to build their confidence before doing the real thing.

As we move into 2017, where do you think the industry's priorities should lie?

The cost of biologics must be reduced to improve patient access. Part of the answer is to reduce manufacturing costs; for example, by adopting continuous manufacturing and single-use technology. Some companies, however, are fearful of changing their legacy processes. Change will require greater collaboration between equipment vendors, manufacturing companies and – very importantly – regulators.

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