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the Medicine Maker™

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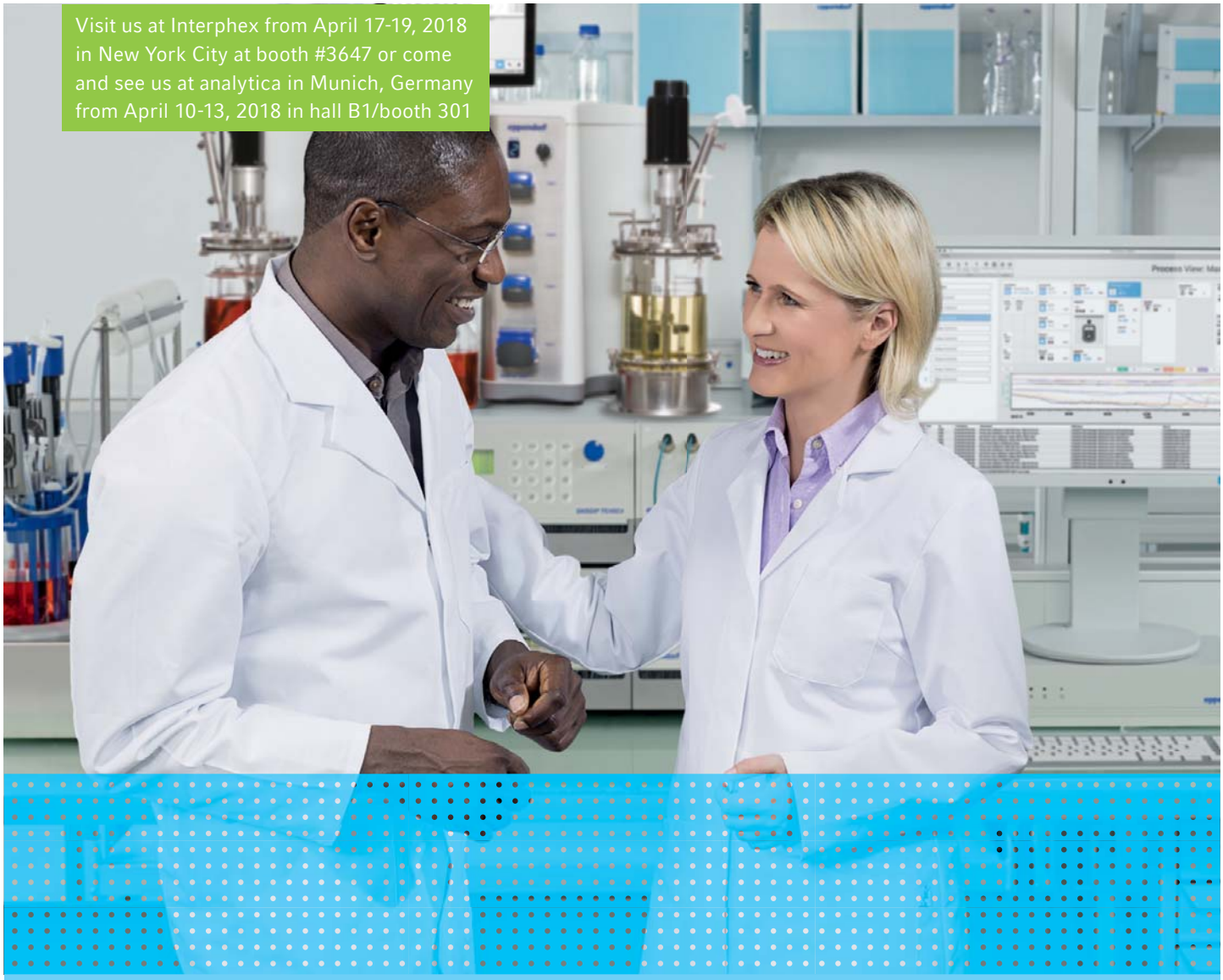

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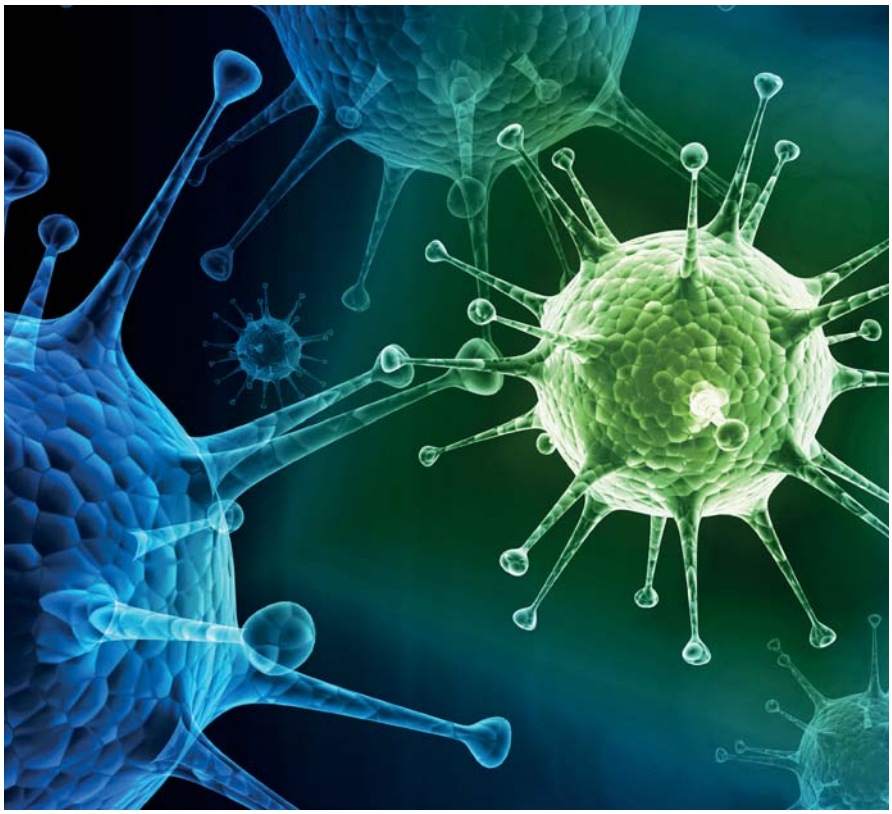

And The Winner Is…

In December 2017, 15 top technologies for drug development were selected for The Medicine Maker 2017 Innovation Awards (http://bit.ly/2m1JCRu). But which is the most groundbreaking? We asked for your opinion on the matter by asking you to vote for your top technology – and vote you did in earnest! We received thousands of votes from all over the world, but the results are finally in.

2017 Winner

- H3N2 Challenge Virus (SGS) – an influenza virus for use as a challenge agent.

2017 Runners Up

- HakoBio (OUAT!) – a 3D and digital reality space for simulating processes and plants.
- MabSelect PrismA (GE Healthcare) – a protein A resin to boost monoclonal antibody purification capacity.

Look forward to hearing more about these innovations in a future issue of The Medicine Maker!

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the Medicine Maker

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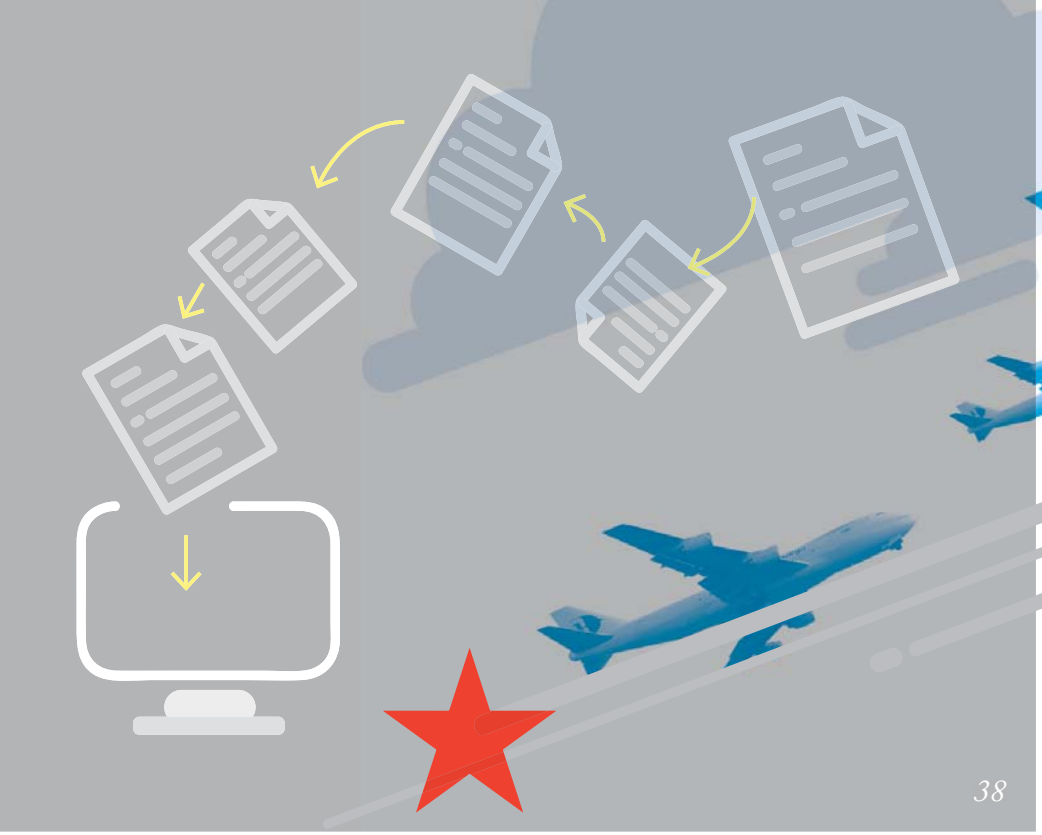

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Calling Time on Bad Behavior

The pharma industry is no stranger to the issue of sexual harassment, but companies are now taking a more public stance on the matter

The #MeToo and Time's Up movements have made sexual harassment a global conversation. Women from all walks of life have become emboldened to speak up – including in the life sciences and pharma industries.

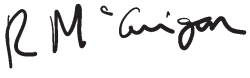
I am the newest addition to The Medicine Maker team (Deputy Editor from January 2018) and, as a woman, I have been watching as the #MeToo movement hits the industry. It has become increasingly evident in recent months that sexual harassment in all industries can be swept under the carpet – or, even worse, result in a backlash against women who speak up. But what I have seen so far in pharma is heartening. Sanofi, for example, got caught up in the French version of the #MeToo movement (also known as #BalanceTonPorc) when it fired director of press relations Jean-Marc Podvin amid a number of allegations. Podvin went on to bring an unfair dismissal lawsuit against Sanofi – and lost. The company did not comment directly on the case, but said in a statement that it has "always taken all the necessary measures to prevent sexual harassment, to put an end to it and sanction it" (1).

Several pharma companies were also amongst 22 advertisers who pulled their ads from a US talk show hosted by Bill O'Reilly in April 2017, after a report in The New York Times revealed that five women had received substantial settlements after making allegations (2). Notably, GlaxoSmithKline joined the ad freeze on the same day that Emma Walmsley took over as CEO (3). (O'Reilly went on to lose his job at Fox News.)

Unfortunately, accusations of sexual harassment continue to emerge. In early March, allegations from a former employee of Janssen Korea came to light, detailing seven years of verbal and physical harassment at the hands of senior employees and client doctors (4). At the time of publication, the story is still developing and Janssen had yet to comment.

As the #MeToo movement builds even more momentum, let's hope all industries listen seriously to any concerns raised, while working hard to celebrate and champion both men and women. Things are changing for women the world over – and it looks like pharma is committed to being part of that.

Roisin McGuigan
Deputy Editor



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Upfront

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

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

First in Class

Pharma steals the two top spots in a ranking of the best online corporate communications

The pharma industry has been a slow adopter of social media – an issue The Medicine Maker covered back in 2014 (1). Now, two pharma companies, GlaxoSmithKline and Bayer, have come first and second, respectively, in a ranking of online corporate performance. What happened?

The annual Index of Online Excellence, produced by Bowen Craggs & Co, a research and consultancy group specializing in corporate communications, for the last 12 years, covers all online corporate communications channels – websites, social media, and apps. The final list is drawn from the Bowen Craggs subscriber database, and contains scores and best practice from more than 100 global companies.

"We created this ranking for one clear reason: to identify best practice in all areas of online corporate communications, so companies can learn from it," says Scott Payton, Managing Partner of Bowen Craggs & Co.

The last time a pharma company came in at number one was almost 10 years ago – Roche in 2009. And Roche remains a strong contender, making number eight in 2018. Does this mean the tide is turning for pharma? The authors of the Bowen Craggs report think so; signs point to a change in larger companies who have historically failed to allocate adequate resources to their online presence – a mistake, says Payton.

"I believe that a corporate website is the most powerful and important 'publication' that any company has in terms of readership, global reach, size and influence. For pharma companies, reputation management is a business-critical issue. And a strong online presence is the most powerful tool for safeguarding and boosting a pharma company's reputation in the world at large," says Payton. "As a general rule, companies that take reputation management seriously invest time, thought and money into online corporate communications – and have the best online estates."

So what makes for a truly excellent online presence? Bowen Craggs judges companies across eight metrics:

1. Construction: covering navigation, ease of user orientation, integration, quality of internal search engine and Google visibility
2. Message: covering strength of home page, visual impact, internationalism and quality of company information
3. Contact provisions: covering the prominence and quality of phone, email and social media contact points for all audience groups online – as well as "self-service provisions" like FAQs
4. Serving society: covering corporate governance information, service for CSR professionals and reputation-building material as a whole
5. Serving investors: covering service for analysts who follow the company, service for those researching it, and private investors
6. Serving media professionals: covering quality of the press release provision, press contacts, press briefing materials and image library

7. Serving jobseekers
8. Serving customers

Twenty-six sub-metrics are also taken into account. And to be in with a chance of a top spot on the final list, companies must excel in all areas – easier said than done. According to Bowen Craggs, for large multinational companies, including those in the pharma sector, the key to an effective online presence is to have a well-resourced central web and social media team with the mandate – and budget – to coordinate global online corporate communications across all the channels used.

"One common mistake is to invest a load of money into a corporate website redesign, and then fail to manage and refine the shiny new site properly on an ongoing basis," explains Payton. "Another common mistake is to fail to manage the corporate website and social media channels in a joined-up way. Many companies have one team managing their corporate website, and a separate one managing social media channels. This is a recipe for fragmentation and duplication. Messages become garbled and money is wasted."

The full ranking can be downloaded from bit.ly/BCRanking.

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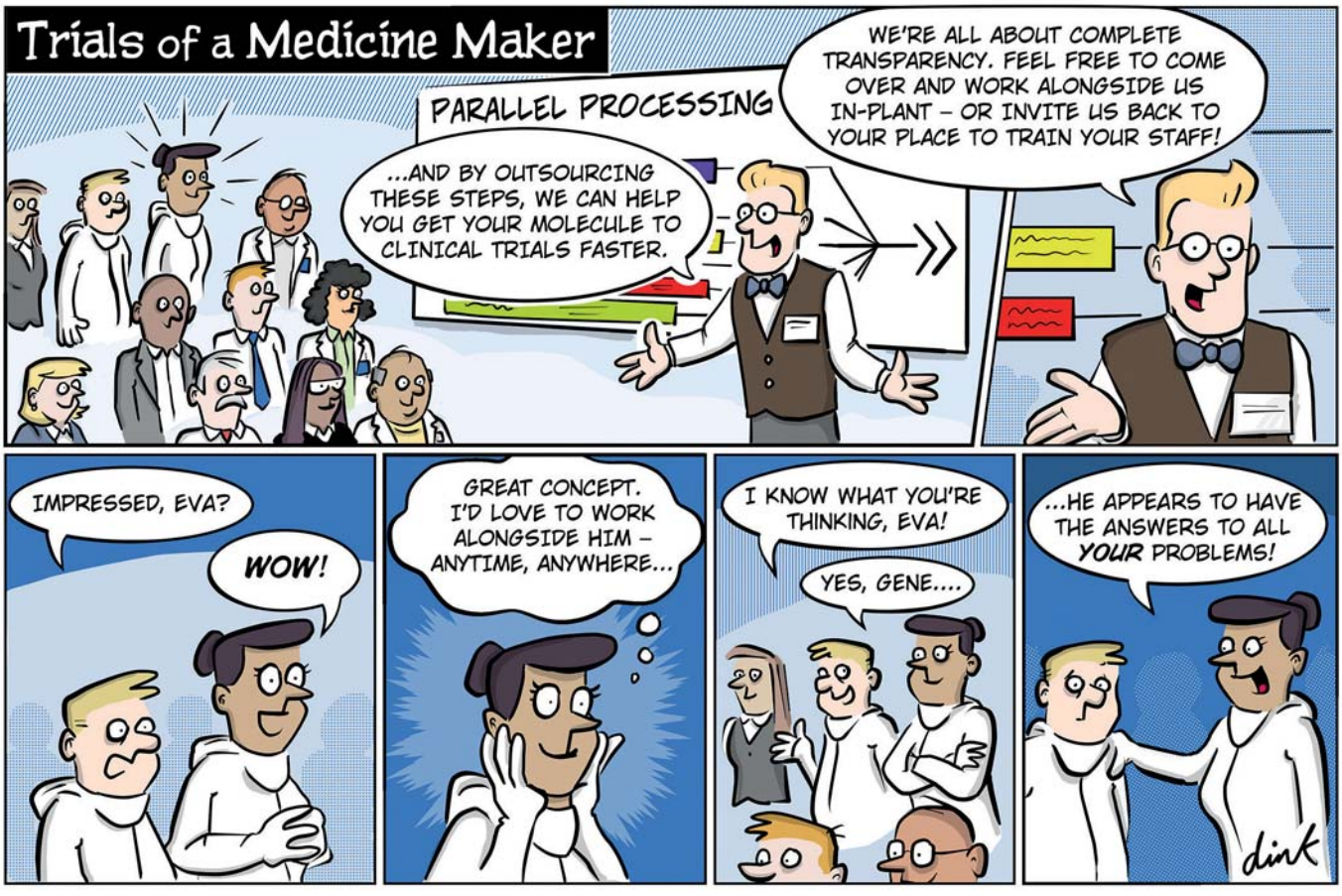

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Ancient Herbs with Modern Promise?

Traditional Chinese medicine is viewed with suspicion by mainstream healthcare, but a new collaboration aims to put ancient ingredients to the test

Do traditional Chinese medicines (TCM) actually work? Scientific proof is often sorely lacking. Nevertheless, even if a medical practice is unproven, the potential for truth is worth investigating. Enter a new collaboration between Elsevier and Beijing University of Chinese Medicine (BUCM), looking at whether TCM represents a rich source of material for further study by mainstream medicine (1).

There is some precedent for seemingly strange and ancient practices proving to be more effective than scientists might expect; for example, an Anglo-Saxon antibiotic recipe calls for bile from a cow's gall bladder – and it's surprisingly effective at killing bacteria (2). And TCM does have some links to modern medicine: "A great example is artemisinin, an active ingredient from the Chinese herb Qing Hao. It was traditionally used for treating fever, but later was developed as an anti-malarial drug," says Jianping Liu, Professor and director of Evidence-Based Chinese Medicine at BUCM. "The Nobel Prize was awarded for this success to the Chinese scholar Tu Youyou in 2015. Artemisinin has saved millions of lives and is one of the most significant contributions of China and TCM to improving global health."

With traditional remedies, it can be difficult to separate effective ingredients from superstitions, so the Elsevier/BUCM effort will aim to create a new taxonomy to consolidate and expand on existing TCM knowledge in Embase, Elsevier's biomedical database. "BUCM, along with Elsevier, is not promoting TCM – but collaborating to share information and create taxonomies that could assist researchers, and lead to better health in the 21st century," says Ivan Krstic, Senior Product Development Manager of Embase at Elsevier.

According to Krstic, some of the largest pharma companies are already interested in exploring how TCM can aid drug discovery and the development of new therapies. "Our collaboration aims to make existing research around TCM more discoverable, allowing drug researchers to seek knowledge from traditional clinical practices for modern biomedical sciences," he adds.

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Hurt Blocker

Researchers develop a new way to tackle pain: inhibition of RNA-protein interactions

"There's a tremendous need to better understand the molecular mechanisms responsible for pain," says Zachary Campbell, Assistant Professor at the University of Texas at Dallas. His team has been delving into the chemical cascade that leads to pain perception – and aims to intervene by inhibiting a key protein – Poly(A)-binding protein (PABP) – using a synthetic RNA mimic.

The result was reduced pain sensitization in mice (1). PABP binds to the Poly(A) tail of messenger RNA during the formation of multiprotein complexes that regulate transcription during protein synthesis. Previous studies have found that one of those complexes, the cap-binding complex, is a key player in pain sensitization. The researchers used functional genomics to examine the specificity of PABP, and then created a chemically stabilized RNA substrate that could bind PABP and inhibit translation, which prevents the formation of the cap-binding complex – and cuts the pain response.

PABP is expressed throughout the peripheral nervous system. According to Campbell, the study results show that the team's 'Poly(A) SPOT-ON' approach impairs pain sensitization in multiple models of tissue injury in vivo. "To the best of our knowledge, our work is also the first to describe the use of chemically modified substrate decoys suitable for in vivo use as translation inhibitors," says Campbell.

He also adds that it is "highly unlikely" that the effects of the SPOT-ON are mediated by the central nervous system because the researchers injected the compounds at the site of an injury at a low dosage. "The use of local administration near or at the site of an injury as a means of preventing long-term pain memories has tremendous potential in certain contexts, such as surgery."

Given the mechanism of action, Campbell suggests that the approach could have clear advantages over opioids.

Reference

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Towards Transparency

Health Technology Assessments are a way of life for the pharma industry, but are all HTAs equal?

Health Technology Assessment (HTA) bodies evaluate whether new medical technologies, such as pharmaceuticals or medical devices, represent "good value for money" for national public payer institutions. Naturally, transparency is important; HTAs must assure a level playing field between various stakeholders involved in evaluating medical technologies and also ensure that decisions are sound and taken based only on the best available scientific evidence.

Piotr Ozieranski, a lecturer in the Department of Social and Policy Sciences at the University of Bath, is particularly interested in the Polish healthcare system. Despite being one of Europe's largest pharmaceutical markets, Poland has had some trouble with conflicts of interest when it comes to drug evaluations. Ozieranski's previous research pointed to challenges in Poland around drug company lobbying, both direct and via seemingly independent third parties, such as patient organizations, as well as conflicts of interests of experts and public officials working for the Ministry of Health and the Agency for Health Technology Assessment (AHTAPol).

In a new study, a multi-institutional team wanted to know whether there had been any improvement in the country over time. Ozieranski explains the results...

How do HTAs work?

Evaluations undertaken by HTA bodies are complex, and involve clinical and economic data (cost-effectiveness and budgetary impact analyses) – and sometimes ethical considerations. The outcomes of these processes may be informed by explicit thresholds of cost effectiveness; for example, NICE in England will normally approve drugs whose cost effectiveness falls between £20,000 and £30,000 per quality-adjusted life year gained; in Poland the cost effectiveness threshold is three times GDP per capita.

It's also important to note that the evaluation of medical technologies by HTA bodies usually involves two phases: i) assessment – an earlier and more technical phase, primarily driven by health economists, that focuses on analyzing data submitted by manufacturers; and ii) appraisal, which draws on the outcomes of the assessment phase but also involves a range of external stakeholders, such as clinicians and patient experts. In our study, we focused on the assessment phase, which is a new development in research on HTA, as most studies with a social science perspective focus on the appraisal phase and, in particular, on the operation of appraisal committees.

Has the situation in Poland improved?

The transparency of AHTAPol's assessment reports has, in many ways, reached the transparency standards set out by NICE. A key indication of this is that the AHTAPol has redacted a decreasing share of its assessment reports (these redactions are normally requested by manufacturers to protect their commercial interests).

Perhaps surprisingly, and certainly against our initial expectations, the AHTAPol turned out to be more transparent than NICE in certain aspects of the HTA process, such as providing summaries of expert opinions and explaining rationales for redacting assessment reports (in other words, the AHTAPol tends to be clearer than NICE in explaining why certain parts of reports have been redacted).

That said, the AHTAPol is still less transparent in other areas of the HTA process, such as including information on expert potential conflicts of interest. More specifically, it is often difficult to ascertain how many experts whose opinions were considered in assessment reports, had reported any potential conflicts of interest, and of what kind (or how serious these potential conflicts of interest had been). NICE, by contrast, is considerably more open in this respect – we know which experts reported potential conflicts of interest and what their nature was.

Importantly, these findings are consistent with our earlier research around the challenges associated with potential conflicts of interests of some stakeholders in the HTA, and reimbursement processes. The findings also correspond with research funded by the EU commission that shows a high degree of tolerance for conflicts of interest in Poland's healthcare sector more generally.

How closely do HTAs and the pharma industry interact?

When it comes to "light" HTA bodies (such as the Scottish Medicines Consortium, NICE's Single Technology Appraisal process, the AHTAPol), the evidence submitted by drug manufacturers to support their products is the key source of data for HTAs. "Heavy" HTA bodies, by contrast, develop their own analyses from scratch (for example, the multiple technology appraisal process model used by NICE). Light HTA approaches are increasingly prevalent, so the role of industry and its evidence, by implication, is increasing.

Collaborations between the pharmaceutical industry and clinicians or patient advocates often involve financial ties (such as grants or donations). It is, therefore, important that any such potential conflicts of interests are disclosed during the HTA process – this way, it is possible to evaluate whether expert contributions might have been unduly influenced.

Will Irish Eyes Keep Smiling?

"Brexit and Trump" were the talk of Dublin town at the 2018 Biopharma Ambition conference

Delegates from the international biopharma industry gathered just a stone's throw away from Dublin Castle's medieval Record Tower for the Biopharma Ambition conference in February. The biopharma industry is hugely important for Ireland's economy, making up a remarkable 55 percent of Irish goods exports – €67.8 billion in 2017.

Delegates at the conference were told that each of the world's top 10 biopharma companies have a presence in Ireland, and that the island was the sixth largest medicinal and pharmaceutical manufacturing hub in the world in 2017.

Nevertheless, Mary Dickens, President of the Irish Pharmaceutical Healthcare Association and Country Chair & General Manager of General Medicines at Sanofi Ireland, warned against complacency in her welcome address. "The wider environment is not without challenge," she said, referring to a recent government commissioned study highlighting the vulnerability of Irish biopharma to a "hard Brexit," as well as to the Trump administration's recent tax cuts.

Writing for the Irish Examiner, John Whelan, consultant on Irish and international trade – who attended the conference – pointed out that some pharma manufacturers will "find it imperative" to shift plants from Ireland to the UK, given the €4.8 billion of pharmaceuticals that Ireland exports to the UK (1). However, Martin Shanahan, CEO of IDA Ireland, was more optimistic, saying that he's seen a "huge amount of interest" in companies looking to invest in Ireland given potential post-Brexit regulatory challenges.

If divergent regulations lead to non-tariff barriers to trade between the UK and the EU (including Ireland), Ireland may look like an attractive proposition for pharma manufacturers looking to sell into the wider European market. The question is, would new investment compensate for the reduced access to the UK market? And is Ireland's proposition still as attractive for biopharma companies given the changing international tax environment?

Tommy Fanning, Head of Biopharmaceuticals at the IDA, thinks so. "Brexit can yield opportunities for Irish life sciences," he says "We're already seeing some sub-supply services companies beginning to look at Ireland." A number of supply chains are set up so that products are manufactured in Ireland but the final pack and QP release into the European market is done in the UK. "Now the large pharma companies are saying to their partners, 'we need you to have a base in the EU.' And given that Ireland has a large manufacturing base already, it makes sense logistically to put that in Ireland too," he says. "Even the packagers are beginning to put jobs into Ireland – and we had not been talking to packagers for a number of years."

On the subject of US tax cuts, Fanning thinks the jury is out. "Although the big companies in the US are saying they're going to invest their extra cash in the US, they'll also invest some of that cash in their international operations. So I think there's two sides to that picture," he says.

Fanning believes that the secret to Ireland's success in the biopharma space isn't just the attractive tax environment. The main factor, he says, is education. The second is the regulatory environment. "You often read about FDA and EMA warning letters for plants – the plants in Ireland do not get those," he says. "This means companies are confident that their products will be manufactured and delivered on time.

"Everyone talks about tax in an Irish context, but it's the icing on the cake. Unless you have the infrastructure, the skills, and the regulatory environment, no company will come."

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Raising the Biosimilar Banner

FDA Commissioner Scott Gottlieb wants more biosimilars on the US market

At the National Health Policy Conference for America's Health Insurance Plans, FDA Commissioner Scott Gottlieb described how "pernicious" rebating and contracting schemes in the US healthcare system are discouraging biosimilar development. Although explaining that the FDA "doesn't – and shouldn't" regulate drug prices, he explained that helping to ensure access to medicine is a vital part of the agency's role. Here are some key quotes taken from his speech (1).

Why the US needs biosimilars

- "Biosimilars not only present opportunities for significant cost savings, they can dramatically expand patient access to therapies. One 2017 study from QuintilesIMS – done at the request of the European Commission – found that competition from the introduction of biosimilars in the EU dramatically increased patient access. In fact, the report noted that 'all products in these therapy areas…are contributing to [increased] patient access' as prices fall."

The problem

- "Too often, we see situations where consolidated firms – the PBMs [Pharmacy Benefit Managers], the distributors, and the drug stores – team up with payors. They use their individual market power to effectively split some of the monopoly rents with large manufacturers and other intermediaries rather than passing on the saving garnered from competition to patients and employers."
- "We've approved nine biosimilars, and five in 2017… only three are currently marketed."
- "When biosimilars launch, their initial discount is typically on the order of 15% or 20%. And unless the plan can switch all their patients over to the biosimilar, the cost of the lost rebates on the patients who remain on the original biologic won't be offset by value of the discount on the biosimilar, and the smaller number of patients who are started on it."
- "PBMs have a significant financial incentive to limit the uptake of biosimilars to continue the flow of large rebate payments. And health plans have a big disincentive to switch to the biosimilar, and lose the incumbent rebates paid on the innovator biologic."
- "Once biosimilar makers see that the system is rigged against them, what's the incentive for a biosimilar maker to pour money into future investments to develop these lower cost alternatives? The rigged payment scheme might quite literally scare competition out of the market altogether."

How do we improve the market for biosimilars?

- "I've been on the record as advocating companies move away from rebate based contracts. I think they actively harm patients in high deductible health plans, or patients who are forced to utilize products on non-preferred tiers. They can find themselves paying coinsurance based on a list price that no insurer pays. In fact, in some cases, a non-insured cash pay patient would pay less – this is certainly not the purpose of having insurance."
- "United Healthcare, one of the nation's largest insurers, announced that it would pass along full drug rebates to more than 7 million people in its fully insured plans starting next year. This is a potentially disruptive step… I hope that others in the industry consider disrupting the current model."
- "The FDA will do its part by laying out an efficient path for showing how biosimilar products can demonstrate interchangeability with their branded counterparts."
- "Payors can also lead the way in formulary design by making biosimilars the default option for newly diagnosed patients… [and] by doing more to educate clinicians about the safety and value of biosimilars, to encourage appropriate adoption."

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Preparing for the Paradigm Shift in Bioprocessing

While upstream titers have improved dramatically over the last decade, downstream processing has remained relatively unchanged. Now is the time to push bioprocess efficiencies even further. In August 2017, Merck acquired Natrix Separations, Inc., a provider of hydrogel membrane products for single-use chromatography. Renaud Jacquemart has been with Natrix since 2011 and today is the Director of Vaccines Process Sciences. Here, he explains how the Natrix® technology could offer a helping hand in next generation bioprocessing.

By Renaud Jacquemart

The exact definition of "next generation bioprocessing" and how that might be implemented varies depending on which company you speak to, but it essentially comes down to improving processes. And I believe it represents a paradigm shift in the industry. Biologic products are not simple to make and biopharma is a conservative industry, so there is not always a willingness to adopt new technologies. However, upstream titers have improved so much that many companies are now looking to embrace change; for example, by retrofitting their facilities to cope with the increased quantities of antibody that they are producing upstream. Some are producing kilograms of antibody per batch, whereas ten years ago they were only producing a few hundred grams; most downstream processes simply aren't built to handle such large quantities, which leads to bottlenecks in purification. In addition to process challenges, there is also increasing pressure on drug costs, with governments, insurance companies and other payers calling for biopharma companies to lower their prices. One example that highlights the issue is Ocrelizumab (Ocrevus, Genentech), approved in May 2017 by the FDA to treat primary progressive multiple sclerosis, with a cost of $65,000 per year. Such high prices put tremendous pressure on health systems, and therefore treatments are discussed not in terms of disease-modifying performance, but in improvement over cost ratios. My team and I have no direct impact on the pricing process but we can at least help manufacturers to develop the best processes possible, which may enable them to lower costs. After all, if you want to sell something at a lower cost, it stands to reason that you first have to produce it at a lower cost.

Continuous manufacturing is a buzzword in the biopharma industry right now because of its potential to intensify processes. By compressing the process into a small footprint that still produces the same quantities as a large-scale facilitate, you benefit from lower upfront investment, lower running costs, and a shorter build time. Right now, however, there are still many questions about how to actually implement a fully continuous bioprocess. Single use is certainly a key enabler of continuous bioprocessing, and in upstream there has been a lot of progress with the introduction of perfusion bioreactors. There are also single-use options for certain unit operations in the downstream process, but one of the missing links was chromatography, which is one of the most expensive steps of the process. In the current paradigm, traditional resin chromatography columns are oversized to match upstream productivity. They are very expensive and require amortization over many production lots, as well as cleaning, storage, validation and significant labor to operate. And they also omit flexibility and agility in the manufacturing.

Forging the way with technology

So how does the Natrix® technology fit into next generation bioprocessing? Merck is committed to establishing a portfolio of next generation bioprocessing technologies that enable faster and more efficient biomanufacturing – and one

of these technologies is the Natrix® Membrane. The Natrix® platform is not the only chromatography option on the market, but our product is unique in that it offers extremely high productivity. Indeed, where other chromatography technologies provide either high binding capacity or high speed, the Natrix® technology features a very high density of binding sites throughout a macroporous 3D structure that provide high productivity, simultaneously. Effectively, you can achieve production-scale capacity – and maintain quality – in a much smaller footprint, allowing you to move away from traditional columns. The technology, which originally came from McMaster University in Ontario (Canada), is made using a single-step polymerization that provides lot-to-lot reproducibility to guarantee consistent performance. And because our technology is single use and fully validated for GMP use, it is treated as a consumable, ready to use in a plug-and-play format.

Before I joined Natrix, I had actually worked with other membrane chromatographic products. Back in the early 2000, when fears of an avian flu pandemic were rife, membrane chromatography was considered by many to be the holy grail because of its potential to accelerate vaccine development, but it didn't take off at the time because we didn't have the right capacities and the industry was not ready to fully adopt single-use technologies. I was really disappointed at the time, but today things are very different – intensified upstream processes deliver large quantities of biologics and patients are waiting: it is time to address the downstream bottlenecks!

The acquisition by Merck has greatly increased the visibility and attractiveness of our technology. Natrix Separations, Inc. is not a small company anymore – it is part of a large, well-established organization that is a leader in purification. I recently gave a presentation at an international, scientific conference and people congratulated me on the deal with Merck, with one individual telling me that they had been investigating the Natrix® technology for some time, but were concerned about the risks of us being a smaller company. Now that we are part of a bigger company, they are happy to move forward because we have provided them with the real solution to address their challenges in therapeutic supplies!

Despite biopharma being a conservative industry, I am seeing a lot of positive activity that implies a willingness to embrace next generation bioprocessing. I am editing a book right now called New Paradigms in Biomanufacturing, but the outline keeps changing because my partners worldwide are making progress so fast! It is really encouraging and shows how much momentum there is around this topic.

Renaud Jacquemart is Director Vaccines Process Sciences at Merck, Burlington, Ontario, Canada.

And Coming Up Next...

The work at Natrix is by no means complete – we are currently developing the second generation of our membranes that will benefit from the addition of affinity ligands. The first product we are working on is a protein A membrane. Protein A ligands have been designed to selectively capture antibodies, therefore reducing the number of process steps required and providing robustness to the process. But many other ligands and applications have largely been ignored. In the future, we envision that all end users will have access to a Natrix® affinity membrane column and achieve the same performance that is obtained with Protein A today. For example, it is possible to make vaccines with the same approach. In this case, a ligand is attached to the base membrane to capture the virus of interest. My team recently published on this strategy (1,2). The performance of the Natrix® products in this context is a huge advantage, but major improvements would not be possible without a holistic approach, combining progress in upstream and downstream, but also facilitating design and analytical/release capabilities.

We are concretely playing a role in helping to make biotherapeutics as well as vaccines more affordable. We currently partner with two world leaders in biomanufacturing innovation: Batavia Biosciences (Leiden, Netherlands) and Univercells (Gosselies, Belgium), with whom we were awarded the Grand Challenge "Innovations in Vaccine Manufacturing for World Markets" by the Bill & Melinda Gates Foundation. In this project, the aim is to develop a new vaccine manufacturing platform that intensifies the process and cuts the cost down to 15 cents per dose. We will use our chromatography membrane platform, Univercells' process intensification and integration technologies, and Batavia's vaccine development and manufacturing capabilities. The initial target is to establish a microfacility for inactivated polio vaccine, but the platform concept could be applied to any viral vaccine to enable the production and distribution of high quality vaccines in low income countries.

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Through the Looking Glass

There is a shocking lack of attention given to racemization in drug discovery, despite it having huge implications on the efficacy – and safety – of drugs. We hope the tool we have developed will be the first step towards change.

By Niek Buurma, Lecturer in Physical Organic Chemistry, School of Chemistry, Cardiff University, UK.

Many drugs are chiral molecules: they have the potential to "flip" and exist as different enantiomers – non-superimposable mirror images of the original molecule with an identical chemical structure. In some cases, this flipping behavior can occur when an enantiomerically pure drug enters the body, in a process known as racemization. Typically, only one of the two enantiomers is useful, meaning that the pharmaceutical action of a significant fraction of all drugs depends on administering the correct enantiomer. The reason why typically only one enantiomer is useful is that biological targets of drugs are usually just one mirror image. Therefore, when we administer a mixture of enantiomers, one will act as intended but the other enantiomer could be a bad fit with the target, leading to this unwanted enantiomer binding to unintended targets, potentially causing serious side effects.

The tragic story of thalidomide is often cited as a reason for the need for enantioselective synthesis in academia, and triggered the current approach to enantiomers in the pharmaceutical industry. Thalidomide, which was discovered by the German company Chemie Grünenthal, was given to women as a mixture of the two mirror images to treat morning sickness in pregnancy. It is often said that the desired enantiomer acts as required, but the second enantiomer is teratogenic and therefore led to severe birth defects. As a result of the thalidomide tragedy, new drugs can no longer be mixtures of two enantiomers – so called racemic mixtures – unless the effects of both enantiomers have been studied fully.

Today, almost everyone is aware of the need to administer single enantiomer drugs – and enormous amounts of time and money are invested in the development of synthetic routes to make single enantiomers. In fact, syntheses producing racemic mixtures have become all but unpublishable.

But even if single enantiomers are synthesized there is a risk for the pharmaceutical industry; if the enantiomer racemizes and racemization is discovered late in the drug discovery process, the compound becomes a dead end, wasting precious

"The tragic story of thalidomide is often cited as a reason for the need for enantioselective synthesis."

"If racemization is discovered late in the drug discovery process, the compound becomes a dead end, wasting precious time and money."

time and money. And it's not only in drug design where racemization is a risk; in the identification of new natural compounds, one also needs to be aware of the risk that stereogenic centers may have racemized. Similarly, probe molecules are used a lot in biological chemistry, system biology, and so on – and these, too, can racemize.

Despite how crucial racemization is in a number of fields, there have been no good models to quantitatively predict how these enantiomers will behave once exposed to aqueous conditions in the body. The absence of good workable tools appears to have generated an attitude where the risk was readily swept under the proverbial carpet. In fairness, studying racemization isn't simple; it requires the right equipment as well as dedicated fundamental studies of the kinetics and mechanisms of racemization reactions. My attention was drawn to this blind spot through conversations with a friend who worked at AstraZeneca. When we started to look for data to start to predict racemization risk, we discovered there was almost none available in the literature, which came as a real shock! We therefore set out to generate the data we needed. To develop a predictive model, we needed a significant experimental dataset, which three PhD students acquired over roughly ten years. We also needed the right project team. Our predictive model required a correlation between results from kinetic studies in my group in Cardiff with data from computational work in the Leach group at Liverpool John Moores University; without either set of data, there is no correlation. Without correlation, there is no prediction. Finding funding for these kinds of fundamental studies is not always easy – but fortunately our sponsors, including AstraZeneca, recognized the importance of this work.

We have already received enquiries to study molecules potentially at risk and we are looking into these compounds now. We're also developing a version of the model that predicts the risk of racemization during typical reaction workup procedures, and whether enantiomeric excess may have been lost during purification.

In my view, our guidelines and models provide an excellent approach to predicting racemization (1). We would like to see our quantitative predictions and experimental tests – what we consider much-needed tools – incorporated as standard in the drug discovery pipeline. Our hope is that the availability of these tools should lead to researchers being less inclined to sweep racemization risk under the carpet, helping to avoid dead ends, and design out racemization risk at an early stage of the drug discovery process.

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All About the Box

Patient adherence is a known issue, but what role does packaging play?

By Tiffany Overstreet, Global Category Director at Essentra, UK.

Approximately 50 percent of patients with chronic diseases in developed countries do not take their medication as prescribed – a significant problem for both patients themselves and the healthcare sector overall. Shockingly, the percentage is even higher in developing countries. Research in the UK alone shows that non-adherence can cost the National Health Service £500 million a year – broadly equivalent to funding 30,000 kidney transplants or an additional 21,000 qualified nurses.

Patient adherence affects the whole industry, so every stakeholder should do their bit to help. Drug developers, for example, can design medicines that are easy to take with reduced side effects – but that may be easier said than done. So what else can be done to improve adherence? In my view, one of the simplest changes revolves around the practice of packaging design. If we provided patients with more digestible and accessible information on side effects, ingredients and how a treatment actually works, perhaps patients would be more inclined to take medicine adherence seriously because they would better understand that medicines only work if you take them correctly.

Typical primary packaging does not always have enough space for extra information, but it's straightforward to supply multi-fold leaflets or extended contents labels. It almost goes without saying that all long-form information should be presented in the clearest format possible; text should be printed in a legible font face and size, and visual features, such as images or charts can be used to really help emphasize certain facts. All the information needs to be easy to navigate – the use of symbols, shapes and color can help in this regard by encouraging greater engagement and understanding.

"In my opinion, too few manufacturers have considered smart packaging that indicates dosage unit and dates."

In addition to a lack of knowledge, patient forgetfulness and time constraints also negatively affect patient adherence (how many of us have forgotten to take our medicine?). It is one thing to understand the need and benefits of taking medication at the correct intervals, but it is quite another to remember to actually consume them. In my opinion, too few manufacturers have considered smart packaging that indicates dosage unit and dates. What about calendarized packaging? What about intelligent packaging that monitors consumption and alerts consumers that haven't taken their medicine through a smartphone app? And yes – these innovations do exist! The problem is that they are not considered often enough.

How innovative packaging design can be – particularly for prescription medicines – depends on legislation. For example, the EU's Falsified Medicines Directive mandates the inclusion of a number of packaging features, which limit the amount of space for packaging

"There are far more packaging options out there than you might expect..."

manufacturers to be creative in their designs. However, I actually see this as more of an opportunity than a challenge because it really encourages creative thinking. Unlike over the counter packaging (where bright colors and designs that help medicines stand out on the shelf are the goal), the differentiation for prescription packaging should rely on value-add features that increase compliance and adherence.

Packaging itself has always played an important role in protecting medicine, but today there is growing recognition of the added value that good packaging can provide. In general terms, packaging should perform five simple tasks: hold its contents, physically protect its contents, communicate information about its contents, provide security to its contents, and aid in the transportation of its contents. Healthcare packaging must fulfil all of those qualities, whilst also trying to make the patient experience as easy as possible. And good pharmaceutical packaging should also ensure that patients are supported throughout every touch point. There are far more packaging options out there than you might expect to help you meet all the objectives – but note that there is rarely one ideal solution for all patients.

Last year, we developed a 'Patient Adherence Pack' to showcase some of the features that drug manufacturers could consider. It is not a commercial product, but rather an example of how packaging could help promote adherence using infographics, portable alert cards and other features. I believe it is vitally important to get the industry thinking more about what can be done to tackle the non-adherence issue – and packaging has a role to play.

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PHARMA LOGISTICS: UP IN THE AIR OR IN DEEP WATER?

Tens of billions of dollars' worth of (bio)pharmaceuticals are scrapped every year because of logistical hitches. What can be done to improve the situation? And which mode of transport – air or sea – should companies choose?

By James Strachan, Deputy Editor

What could be simpler than moving products from point A to point B? A great deal, as it turns out – especially when your product is a sensitive chemical compound or biological.

Shippers from all sectors have to deal with warehousing, transportation, customs clearance and regulatory compliance as they transport their goods across the world (easier said than done). But pharma companies also have to maintain a strict cold chain, where temperature excursions can ruin millions of dollars' worth of drug – not to mention the potential impact on patients.

A staggering $35 billion worth of pharma products are scrapped every year (see our sidebar: What a Waste on page 29), and 30 percent of those losses are attributable to logistics issues alone. During the journey from point A to point B, there are numerous hand-offs and opportunities for things to go wrong. In this feature, you'll hear about pallets being left for days in the baking Dubai heat, communication mishaps, and unexpected bankruptcies...

Given the challenges posed by the logistics process, choosing the right method of transport is crucial. There are advantages and disadvantages to both air and sea freight: with sea generally saving on cost, and air being a quicker option that is more prone to temperature excursions. Recently, analysts have suggested that cost pressures and reliability issues have led pharma away from airfreight, which is instead taking to the seas. But as the industry shifts towards complex biologics and personalized therapies, will the trend continue? And what impact will new cold chain technologies and data monitoring systems have?

Much has changed for the logistics industry over the past half a century, with pharma supply chains becoming increasingly international. And as emerging markets continue to develop regulatory infrastructure – further globalizing pharma supply chains – predicting the dominant mode of travel is no easy feat. Here, we speak with experts from within the logistics industry – from both sides of the air versus sea debate – to assess where pharma's future lies.

Pharma Logistics 101: Up, Up and Away?

Alan Kennedy is the founder and executive director of Pharma TEAM-UP, a not-for-profit organization seeking to get pharma companies working together on logistics. Here, Kennedy gives an introduction to the sector and discusses where improvements could be made.

Keeping meticulously manufactured pharmaceutical products in tip-top (aka undamaged and therapeutically effective) condition during their long and often arduous journey to market can be a complex, risky, and expensive business. Once outside the sterile surroundings of a manufacturing or filling environment, the risk of product contamination or deterioration escalates dramatically. The lower deck conditions of a Boeing plane or the inside of a typical intermodal freight container are a long way from the GMP-validated cleanrooms and controlled laminar-flow environments of the pharma production environment. The handling of temperature-controlled pharmaceutical products in particular is a complicated business and presents unique challenges. According to the International Air Transport Association (IATA), the global pharmaceuticals logistics market is valued at $64 billion and is one of the most regulated, expensive and fragile cargo markets in the world today.

Pharma logistics usually involves one or a combination of three different transport modes:

- Road – by far the most widespread method (air and sea freight both involve road feeder steps).
- Air – used for a high proportion of very-long-distance and intercontinental distribution on account of its speed and flexibility, but it is expensive.
- Ocean – there has been a substantial shift of intercontinental pharma freight from air to sea over the past five years. Sea freight is a fraction of the cost (around 20 – 25 percent) of air and is inherently safer and more reliable. One company in the vanguard of this modal shift is AstraZeneca, which has succeeded in moving their air to sea ratio from 19:1 in 2012 to 3:7 today (or, in other words, they have moved from having 5 percent ocean freight in 2012 to 70 percent in 2018).

There is also a very small volume of pharma that travels by rail. However, this may change over the coming years as the "New Silk Road" (and rail) route between Asia and Europe is established.

I remember a time when pharma logistics was pharma's "forgotten baby." The physical distribution element of the pharma supply chain was perceived as a necessary evil and, as its impact on overall cost was relatively low, top management paid it scant attention. Fast-forward to the present and logistics is rapidly becoming about much more than just cost, capability, and rates. Recently, growing regulatory and financial pressures, plus the need to address a very high – and seemingly intractable – incidence of product deterioration during transportation, has forced companies to think hard about logistics. In fact, the industry is beginning to recognize the potential for logistics as a value-creating process as opposed to a perpetual cash-drain. This new focus is partly a result of the success of supply-chain driven companies, such as Inditex and Amazon – the latter has based its entire business around disrupting logistics models. And before too long, the digital revolution and other technical progress will shake up the logistics status quo – and in a big way!

I believe big data and new technology is going to transform pharma logistics. By harnessing, and often combining, the latest technologies, many doors to hitherto stubborn problems will open. Real-time track, trace and temperature monitoring, end-to-end supply chain integration, omni-channel supply models, demand-based/make-to-order supply systems, value-based alternative-care models and innovative pricing/payment systems are just some of the solutions that require modern technology to succeed. Blockchain is another high-profile technology that holds much potential for securing supply chains and their associated transactional ledgers (if the digital community's promises in this regard stack-up in practice).

"Blockchain is another high-profile technology that holds much potential for securing supply chains and their associated transactional ledgers."

Big data acquisition and analysis, together with "evidence-based medicine" have serious implications for cost and time reductions, new product development and optimized offerings, as well as smarter business decision making. Some supply chain areas of big data application include performance improvements in temperature, location, and security, as well as demand fulfilment and generation, such as real-time sensors, stock-movement information, patient diagnosis, drug efficacy data, and so on.

You may be thinking all of this sounds very exciting and positive – and it is, but with the availability of mass supply chain data comes the need for intelligent interpretation of the continuous information stream. A greater problem is the fact that pharma

and logistics are very uneasy bedfellows. The combination of the congenitally risk-averse pharma industry with the notoriously stubborn, slow to change and highly fragmented logistics industry is not exactly a marriage made in heaven! An example of the latter is the adoption of the common, digital airway bill (e-AWB); despite the logically unassailable benefits of switching from paper-based airway bills to electronic airway bills, the take-up has flat-lined at just 50 percent – after more than a decade of heavy promotion and exhortation from governments and IATA.

The global regulatory environment for pharmaceuticals is also in a state of flux with scrutiny on the increase and global harmonization still a far-off dream. For example, the 2014 revision of the EU Good Distribution practice, which, inter alia, extended regulatory oversight to CRT (controlled room temperature) pharmaceuticals, has had major repercussions and is still being assimilated. Similarly, the consequences of the legislation covering product track, trace and serialization currently being introduced on a staggered basis (and sadly to different specifications) in the US and Europe is proving an even higher hurdle to overcome.

The industry needs to harness its collective strength to resolve many of the huge challenges it faces in today's era of increasing digitization and disruption. Pharmaceutical companies must set aside their deep-rooted "no sleeping with the enemy" mentality founded around competitive fears and misplaced concerns about anti-trust. By taking a few of the by now well-thumbed pages out of the collaboration manuals of more progressive sectors, the pharma industry could get all the visibility, efficiency, agility, customer-centricity and control that it needs. And though the majority of pharma businesses in this field will, no doubt, be unable or unwilling to rise to the occasion, those that do will be opening the doors to huge opportunities and an unquestionable competitive advantage.

The Poseidon Adventure

Lacking sufficient product to fill a container is a major sticking point for pharma companies looking to move to sea freight. Poseidon consolidates small loads with other pharmaceuticals and sends them on a dedicated pharmaceutical service.

With Alan Kennedy

Poseidon came about from a small meeting of like-minded individuals at the European Temperature Controlled Logistics Conference in January 2017. The consensus? Supply chain stakeholders would need to become more intimately aligned if there was to be any degree of across-the-board improvement in the pharma cold chain.

The Poseidon reform model was conceived and built around some of the principles of supply chain collaboration and integration that are being successfully applied in other industries. Poseidon takes the form of a supply network (as opposed to a supply chain), comprising all the actors involved in transporting a pharma product. It is a pharmaco-driven program that has been designed from the ground up, with the shipper, the logistics companies and suppliers all sat around the same table as equal partners.

A network partner agreement governs the relationships between all parties and they work together as a single team with common goals, rules and performance incentives. At the heart of the program is the Poseidon Management Group (PMG), a democratic body comprised of senior representatives from each of the participant organizations. The PMG is responsible for the strategic direction of the program, while an additional neutral company manages the operational side of the initiative and provides a "filter and sanitize" function to facilitate the sharing of data, the consolidation of shipping loads, and the sharing of assets.

Poseidon is a very important development because it is the very first time that an end-to-end integrated network has been put in place in the pharma logistics arena. There is always much talk and passion surrounding the idea of supply-chain integration and collaboration but, until now, no-one in pharma logistics has succeeded in translating these aspirations into a viable, scalable, transferable, and sustainable business model; one that is all-inclusive, equitably governed and market focused.

The "Poseidon Adventure" that is about to commence rewrites the rules around pharma sea freight and the logistics supply chain. The organizations that are supporting this initiative deserve huge credit for putting their faith and energy behind this momentous collaboration initiative, which has the potential to remedy many of the ills now facing the pharma sector. In addition, the Poseidon model will hopefully be a stimulus and a template for others in their quest for more efficient, more competitive and more concerted supply chains that are fit for purpose in today's rapidly changing environment.

Is the Tide Turning?

Mark Edwards, former Global Freight and Compliance Manager for Actavis and Managing Director of supply chain consultancy Modalis, argues that pharma companies should transport the majority of their products via sea.

I see the momentum in the pharma industry swinging towards sea freight, which is growing at around nine percent per year – far outstripping growth in airfreight. The main advantage is an increase in quality: airfreight has many "hand-offs" where the product is physically handled by different parties, not all of whom are trained in the handling of pharmaceuticals. With sea freight, once the container doors are shut (at the manufacturer's own premises) that is usually the last time the product is touched by anyone until it reaches the customer. The second advantage is cost: sea freight is one-tenth the price of airfreight. Finally, when you transport a product via sea it is sealed and locked in a container with little opportunity for theft. Airfreight, on the other hand, is more open to unwanted intervention.

Despite these three advantages, there are some considerations one must make before deciding to ship via sea: timescale being a big one. The typical sea voyage between Europe and the US is seven to 10 days; from Europe to India and the Far East it's 21 to 25 days; and to Australia it is six weeks. During these long trips, there are one or two risk points when the reefer (temperature controlled) container is unplugged, but this can be mitigated by using thermal blankets or passive protection. That said, the potential for temperature excursions is far greater when transporting via air – even the International Air Transport Association (IATA) has referred to the airport as a "black hole." Temperature problems at sea do arise, but they are relatively easy to predict and protect against.

Sea Versus Air

Amy Shortman, Chief Executive Officer, ASC Associates, and Cathy Morrow Robertson, Founder and Head Analyst of Logistics Trends & Insights LLC, respectively, wade into the logistics debate

Amy Shortman: The movement of pharmaceutical products via ocean has only begun to gain momentum. As health authorities have increased pressure to reduce prices, manufacturers have been forced to lower their own costs and turn to the relatively affordable option that sea freight offers. Some shipping lines have embraced this new opportunity and are slowly working towards good distribution compliance (GDP).

In fact, moving products via sea can be up to 80 percent cheaper than airfreight. It also provides a more robust method of transportation, especially when it comes to temperature management. The use of reefer containers to ship pharmaceuticals can maintain product temperatures for the duration of the transit, with limited risk of temperature excursions. When it comes to air shipping, there are many variables as the different stakeholders involved in airport infrastructure across the globe introduce the potential for temperature changes.

The biggest disadvantage to sea freight is that it takes significantly more time than air. Another disadvantage is that there are, as of yet, no global standards in place regarding how pharmaceutical products should be handled by the shipping lines and port operations. In comparison, the airfreight industry operates under a global standard: the IATA CEIV Pharma program.

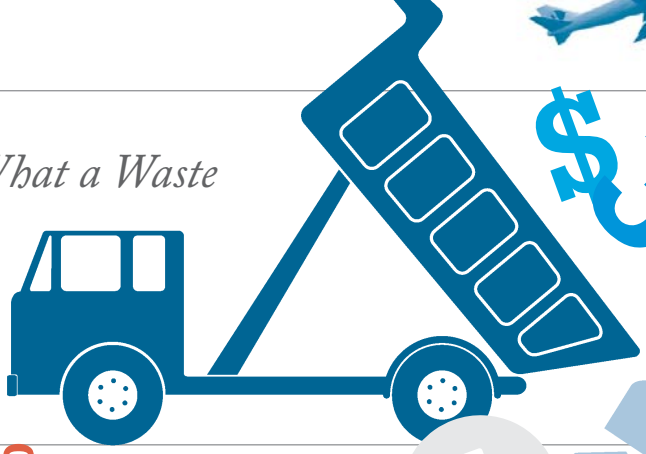
With the sheer number of service providers in the sea freight chain – along with a lack of standardized protocols (each port has its own way of operating, complicating the process significantly) – it will be interesting to see how things develop over the next few years.

Cathy Morrow Robertson: I certainly see a shift towards sea freight and I believe that both the shipping lines and port authorities will embrace and adopt elements of the GDP guidelines and train their staff to an appropriate level for pharma. For pharma companies trying to work out whether they should be shipping via sea or air, clearly cost-to-ship and the time-in-transit are key considerations. Long transit times could affect the integrity of the product, but for those that do not require special handling, such as some generics, over-the-counter medicines and so on, ocean freight presents some clear advantages. Airfreight will continue to be used for higher value goods.

The cost implications of moving goods by air has driven the increased interest in using ocean freight – and several pharma companies have shifted more goods towards ocean freight. A persistent problem, however, is that some ports are not equipped with enough charging stations for containers to maintain required temperatures prior to being picked up by truck or rail. For that, qualified and trained staff is needed.

I'm still partial to airfreight because it is faster. But if I was responsible for pharma shipments, I would seriously consider testing ocean freight for some of my products.

What a Waste



$35 billion in pharma products are scrapped annually

25% of scrapped pharmaceuticals can be attributed to logistics issues alone.

30% of vaccines reach their destination degraded because of incorrect shipping.

20% of temp-sensitive products are damaged during transport by a broken cold chain.

Estimates suggest that air is responsible for **80%** of all transport temperature issues, truck **19%**, and sea **1%**.

A pallet of unprotected product on airport tarmac with an ambient temperature of ~70°F (21°C) can quickly reach temperatures above ~130°F (55°C).

$15.2 billion
in lost product cost

$8.6 billion
in root cause analysis

$5.65 billion
in clinical trial loss

$3.65 billion
in replacement costs

$1 billion
in wasted logistics costs

Reference

1. *Cargo Sense, "Cold Chain Shipping Loss in Pharmaceuticals", (2014). Available at: http://bit.ly/2vUvfl2. Accessed 28 February, 2018.*

> "Ultimately, most pharma manufacturers will need a combination of both sea and air."

Sea transport also presents some challenges because of the rules surrounding it, such as a limit on the value of the product that can be placed in a single container; however, these can be side-stepped with indemnities or special insurance products. Shipping lines have woken up to the fact that pharmaceutical companies present well-paying cargo that is consistent through the year and could be considered recession proof, which means they can make a good return if they have the right processes in place. Transport and logistics company Maersk has come up with the "Smart Reefer" concept that uses remote container management to alleviate some of the challenges. For example, if conditions inside the reefer change, on-shore teams will know about it.

Ultimately, most pharma manufacturers will need a combination of both sea and air, but there is no doubt that they should set up their supply chains to move the majority by sea, with air being used only where absolutely necessary.

Need for Speed

Stan Wraight, Senior Executive Director of Strategic Aviation Solutions International and Jan Krems, President of United Cargo, argue that airfreight is the only choice, if speed is your priority. And when it comes to value (as opposed to volume), air rules the waves.

What are the main advantages when transporting products by air?

Stan Wraight: First, speed and security: goods that are worth thousands, sometimes millions, in a single shipment benefit from lower insurances fees, lighter packing, faster payment for goods and so on. Second, lower inventory carrying costs and reduced investment in distribution centers overseas to store inventory. Third, e-commerce service providers are setting new standards in delivery expectations by B2B and B2C clients – and these cannot be met by slower sea freight.

Jan Krems: The central difference between sea and airfreight is that sea is simply a no-go for certain products – it just isn't fast enough. An excellent example of this is the recent increase in the use of personalized or precision medicine, with products tailored to an individual patient based on a number of distinct variables. Globally, our TempControl experts are reporting a rapid rise in the need for quick and immediate transport of these time-sensitive and patient-specific solutions.

Are there many disadvantages compared with shipping by sea?

SW: The major one, of course, is cost – and every shipper or consignee should be doing a "test of time" to see if sea freight really generates the cost saving they think it does – all the benefits above should be compared. Safety and security is another issue; it is no secret that theft is a huge issue and increasingly high-value goods, including pharmaceuticals, are targeted. Airfreight is no exception, so companies must ensure that the airline they've chosen meets the standards

Logistical Nightmares

We've heard some of the shortcomings of pharma logistics, but what happens when things really go wrong?

Stan Wraight: The very first use of air cargo for biomedicals, and the atrocious incidents that occurred in their transportation, was a disaster. It came about because the airlines in the beginning were unaware of what was required, largely because of a lack of communication between airlines, shippers and consignees. Millions of dollars were lost, and one can only imagine the number of potential lives that were lost as a result of those medicines not reaching patients.

Mark Edwards: I've personally seen 36 pallets left on the tarmac at Dubai for two days. Not only was the stock financially valuable, it was also essential; the life-changing drugs were heading to a country where supplies were almost exhausted. The product had to be destroyed because of the effects of +50°C temperatures.

Jan Krems: In terms of impact to the cargo industry and its customers, the biggest logistics disaster was the 2016 bankruptcy of the ocean container shipping line, Hanjin. There were hundreds of thousands of shipments delayed around the world – but worse than delayed, many were stuck on ships for months and neither the shippers nor consignees could get them. The value of the pharma stock that was stranded at sea was enormous.

On a brighter note, last year we managed to mitigate a logistics disaster that could have been much worse: the impact of the hurricanes in Puerto Rico. The airports on the island began to open for arrival of flights of relief supplies and workers while the sea ports were still closed. Specifically, United was able to transport more than 1.7 million pounds of generators and other hurricane relief supplies to impacted areas of Puerto Rico and Texas. Because of United TempControl's presence and operations in San Juan, our experts were able to meet with nearly every major pharma manufacturer on the island to discuss how to alleviate the crisis.

Further disaster: In 1996, Foxmeyer Drug – then the second largest drug distributor in the US – tried to revamp its IT systems and its distribution facilities. Its new ERP system couldn't cope with the volumes, and the highly automated distribution center (DC) in Ohio was riddled with bugs. According to Supply Chain Digest, "An order would be partially shipped due to DC problems. The customer would receive a partial order, and call to complain. Unable to see the rest of the order had shipped on a later truck, the customer service rep would authorize a replacement shipment for a product already on its way to the customer. Tens of millions of dollars in unrecoverable shipping errors ensued."

Sea

Alan Kennedy:
"There is a growing momentum behind a shift from airfreight to ocean freight ('modal shift') as pharma shippers seek to raise quality and lower costs. With the arrival of GDP-compliant small-consignment (LCL) services, with superior insurance arrangements now in place, and with a proven ability for the safe shipment of biologics and high-sensitivity medications, ocean freight should be the automatic default for the long-distance transportation of pharmaceuticals."

Mark Edwards:
"Ultimately most pharma manufacturers will need a combination of both sea and air but there is no doubt that they should set up their supply chains to move the majority by sea – with air being used only where absolutely necessary."

Air

Stan Wraight
"There is no doubt that for high-value pharma (new drugs and trials), air is definitely the better choice. I am convinced that with all the investments that airlines and ground handling companies have made in temperature controlled cargo, a reasonably priced solution can be found in air cargo."

Jan Krems
"Shipping by air is obviously more expensive, but we believe that the benefits in speed, safety, reliability and visibility are worth it. However, we also recognize there are low-margin generic drugs that need a more economical option – products where cost plays a primary role in which mode is chosen. We also recognize that with the continuing growth in the global trade in pharmaceuticals and life science materials, there is business enough for both air and sea modes, and both modes are making essential contributions to global health."

Both

Cathy Robertson
"I'm still partial to airfreight because it is faster. However, if I was responsible for pharma shipments, I would seriously consider testing ocean freight for some of my products."

Amy Shortman
"It all revolves around risk. Typically, if you have low-risk product from a value and temperature perspective, sea freight can be an excellent option to use. If you are moving very high value, highly temperature sensitive pharmaceuticals, then airfreight is the usual mode of preference. These are decisions for the shipper that demand a risk-based approach."

> "Safety and security is another issue; it is no secret that theft is a huge issue and increasingly high-value goods, including pharmaceuticals, are targeted."

set by institutes like TAPA (Transport Asset Protection Association) in all facilities.

JK: There are some "advantages" to the sea mode versus the air mode: the rate per kilo is less, and the capacity of an ocean vessel is much greater than an aircraft. Also, there are some classes of dangerous goods than can't be transported by air.

Is there a move to transport more products by sea?
SW: Some companies were moving to sea, mostly due to incompetence in the logistics chain. This has been largely overcome, but I also hear about insurance liability issues with some sea shipping lines refusing to take more than a certain maximum per vessel, resulting in restrictions that has made air even more attractive going forward. That said, generic/non-time sensitive pharma will move to sea unless the cost/value equation says otherwise.

Compliance and Collaboration

Regulatory changes have brought gradual improvements to pharma logistics, but unless the industry focuses on setting up compliant supply chains with reliable partners – rather than cost alone – wastage will continue to be a problem.

By Amy Shortman, Chief Executive Officer, ASC Associates.

I have been involved in shipping pharmaceutical products for the past 21 years. During this time, there have been gradual and slow improvements, largely brought about through regulatory changes. The most significant changes have been influenced by the EU GDP Guidelines. These "new" guidelines were issued in 2013 and they changed the way the industry, certainly within logistics, handles pharmaceutical shipments.

But there still seems to be a great deal of confusion across the world when it comes to working out which guidelines and licenses apply to each part of the supply chain. Part of the problem comes down to the fact that there is no single global standard. The World Health Organization provides global guidance, but the levels of GDP compliance vary significantly across the world; each country has its own interpretation of exactly what GDP entails, and these are usually influenced by one of three regions: the EU, US, and the rest of the world. Generally speaking, the more advanced the country, the more comprehensive the GDP guidelines will be.

Overall, pharma logistics lag behind other industries. For instance, the processes and technologies developed by the hi-tech industry are only now being adopted by the pharmaceutical industry; hi-tech has been using real-time GPS technology for years and pharma is only now beginning to catch up.

I do think the key to success for pharma is collaboration; and it's great to see the industry improving in that regard. We now see pharmaceutical shippers using the supply chain as the forum for collaboration – this may be in part due to the introduction of the EU GDP guidelines, which puts the emphasis and responsibility on the shipper to ensure that their supply chain is compliant. The only real way of doing this is to communicate with all of the stakeholders, and develop and implement quality agreements and standard operating procedures with all parties.

We are also seeing greater emphasis on outsourcing and, in particular, the use of external supply chain expertise. Developing, monitoring and maintaining processes that are compliant with all major regulatory bodies involved is a crucial task – and it may be beyond the scope of those already employed within a company. Rather than trying to train employees to carry out such duties beyond their current role – or creating a new permanent position within the firm – outsourcing to an independent consultant can be an efficient and cost-effective option. Furthermore, where the supply chain transcends national regulations by crossing international borders, having a local expert for each area traversed is crucial.

I am hoping that the industry will continue to work towards global best practice standards, using GDP guidelines that provide a solid quality system for the movement of pharmaceuticals. Companies need to recognize that investment in strong logistics partners is crucial. Setting up compliant supply chains to avoid damage to products (and the resulting claims) is a better long-term solution for the industry; driving down the price of logistics spend should no longer be the focus.

JK: We see the continuation of the existing trend, where the percentage of goods shipped by sea is much higher by volume, but a much higher percentage of goods by value is shipped by air. The latest figures I remember from Seabury Consulting were an 87:13 split in volumes in favor of sea, but a 79:21 split in value favoring air. Lower-value pharma with more stock, and commoditized medicine with a longer shelf-life, are likely to go by sea. Higher-value drugs and/or active pharma ingredients are much more likely to be transported via air.

How common are temperature excursions during air shipping? And where are problems most likely to occur?

SW: Major incidents in the past have been mostly ramp related, during the offload or on-load process where care and procedures were not in place. Such problems usually stem from people looking for the lowest cost solutions, and not taking into account the fact that proper procedures cost money. There are solutions for air cargo containers that are uniquely designed to accommodate highly sensitive materials, such as pharmaceuticals.

The technology used to prevent temperature excursions is extremely effective; the only hindrance is that everything on board requires either EASA or FAA certification, so it can be time consuming to introduce new technology. But systems do exist for both passive and active monitoring.

Any advice for the pharma industry?

SW: Talk to your airline! Talk to your airlines ground handling agent at entry, transit and arrival ports to ensure that your key performance indicators are known, and processes and procedures are in place; and make sure any forwarder (or other third party involved) is aware and complies with your service requirements. Furthermore, choose an airline that has invested in handling procedures that trace, track and constantly monitor the shipment. Choose the airline that has every element in the supply chain: cargo warehousing quality control at origin and destination, handling on the ramp in a secure and temperature controlled way, and IT that gives you status updates in all stages – including temperature. The pharma industry can help a lot by encouraging their logistics service providers to support initiatives by airports and airlines to raise the quality bar, and insisting on carriers that support these initiatives. Good examples include Mumbai and Schiphol Amsterdam, which are creating a data corridor that allows for the complete monitoring of all temperature data from port to port, and carriers like Emirates, which is creating GDP-compliant facilities.

JK: The pharma industry needs to enhance communication between all participants in the supply chain. Manufacturers, forwarders and carriers all employ dedicated and creative people who can develop solutions to problems, but they need to know what their partners are capable of doing and what each party needs from each other. At United Cargo, while we're not turning away transactional business for TempControl, we feel strongly that long-term partnerships based on trust, a willingness to listen and a genuine interest in contributing to your partner's success is the key to moving the industry forward.

How to Beat the Bottleneck

As the accelerating number of monoclonal antibodies on the market continues to drive higher upstream titers, chromatography resin suppliers must continually strive to improve productivity, quality and overall process economy.

By Kajsa Stridsberg-Fridén

The monoclonal antibody (mAb) field has come a long way since the first therapeutic mAb was commercialized in 1986. As of today, over 60 mAbs have been approved in the US and Europe and sales of mAbs are expected to cross $125 billion by 2020 (1). As the number of mAbs on the market and in development has accelerated over the years, so too have upstream titers. With the increasing upstream titers, the constraints on downstream processing have only increased. The efficient recovery and purification of mAbs from cell culture medium is a critical part of the production process and can contribute significantly to the total manufacturing costs (2). Protein A affinity chromatography is commonly used in the process-scale purification of mAbs because it is an easy, fast and selective procedure for capturing the target protein – often resulting in a greater than 99 percent purity from complex cell culture media in a single step.

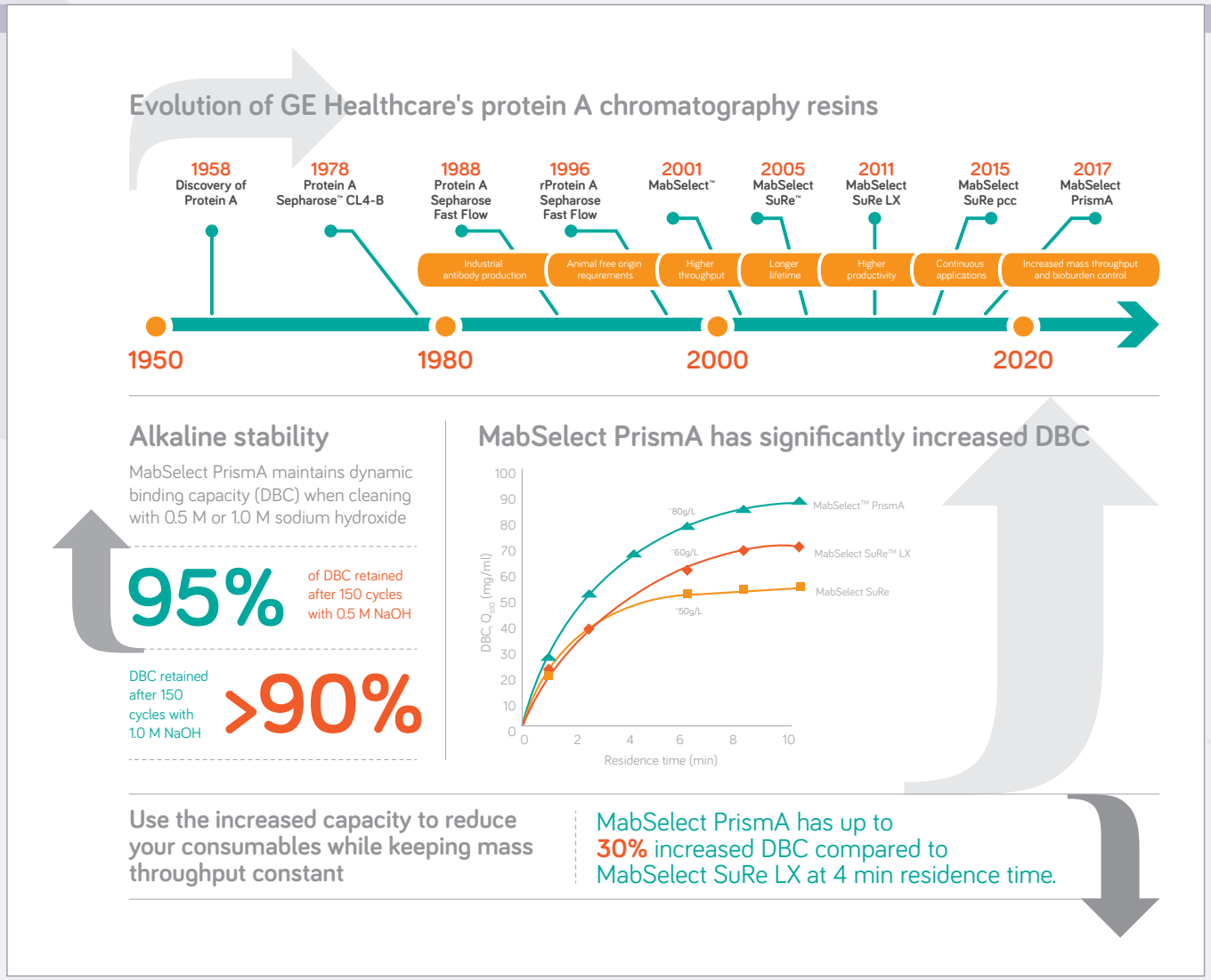
The demands of protein A resins have evolved significantly over the years and the nature of the process means that the capture step can act as a bottleneck – especially as upstream titers continue to increase. I believe suppliers must do what they can to keep pace with the constantly evolving demands of the industry. And this is why GE Healthcare Life Sciences has made the long-term strategic decision to constantly improve our protein A chromatography resins.

Native protein A chromatography resin first began seeing routine use in the lab in the 1980s, but approximately every five years since then there has been a new demand from the industry for further innovation – for resins with new properties to address new challenges. One of the early developments was the switch to recombinant protein A, as the industry moved towards animal-free products. Then, as production scales continued to rise in the early 2000s, we introduced the "second generation" in protein A resins, the MabSelect resin, the first in a family of products, to allow for higher throughput downstream processing.

These resins are based on a highly cross-linked agarose matrix with a recombinant protein A ligand. In 2005, GE launched the MabSelect SuRe resin that has an alkaline-stabilized protein A ligand, which allows for efficient cleaning and sanitization with reagents such as sodium hydroxide (NaOH), eliminating the need for expensive and hazardous cleaning agents. Six years later, we launched MabSelect SuRe LX to meet the needs associated with high-titer upstream processes. One of the key features of MabSelect SuRe LX is its increased dynamic binding capacity (DBC), which allowed better economies of scale. More recently, we've worked to improve the capacity of our protein A chromatography resins to address the industry shift towards continuous manufacturing. MabSelect SuRe pcc further increases capacity at short residence time, making it well-suited for applications requiring fast mass transfer as seen in continuous processes.

Moving forward

The biopharma industry continues to face new challenges, so it is incredibly important to continue to innovate and develop new solutions to support the market. Throughout the evolution of our protein A resins, the need for greater productivity has been a constant theme, and never more so than today. That's why our latest solution, MabSelect PrismA, is designed to achieve high capacity to increase mass throughput, enabling greater productivity of current chromatography columns and systems to be improved without costly capital expenditures (see the infographic for more details). With increased binding capacity, MabSelect PrismA allows for up to 30 percent more target mAb to be purified



using current equipment; alternatively, the resin volume required to achieve a given mass throughput can be reduced.

MabSelect PrismA also seeks to address bioburden challenges with improved alkaline stability to enable more efficient cleaning and prevent growth of microorganisms and inactivate potential endotoxins. Protein A columns are more prone to contamination because of heavy impurity load and weak tolerance for common concentrations of NaOH cleaning-in-place solutions. Regulators are therefore increasingly asking manufacturers to control the sources of bioburden. Improving tolerance for NaOH will continue to pose a significant challenge for the industry in the future.

As we look ahead, it seems likely that upstream titers in mAb production will continue an upward trend. The protein A capture step does create a production bottleneck in downstream processing and it remains to be seen whether current technologies can keep pace. Another major challenge for the field is the development of next-generation antibody constructs. The industry is rapidly moving beyond conventional mAbs towards a variety of new constructs, including antibody fragments, Fc fusion proteins, bispecific antibodies and antibody-fusion proteins. These new antibody variants most often require modifications of the original mAb platform process to enable production. There might also be the potential to modify protein A to create a tailored version based on antibody structure.

Today, we're excited to be talking about our latest chromatography resin, MabsSelect PrismA, but there is always room for further innovation and I have no doubt that we will be sharing the next step in protein A evolution and other affinity chromatography solutions down the road.

Kajsa Stridsberg-Fridén is Senior Project Manager R&D at GE Healthcare, Sweden, and has been with the company for more than 15 years. In her current role, Kajsa is managing cross-functional projects, developing chromatography products for the biopharmaceutical market.

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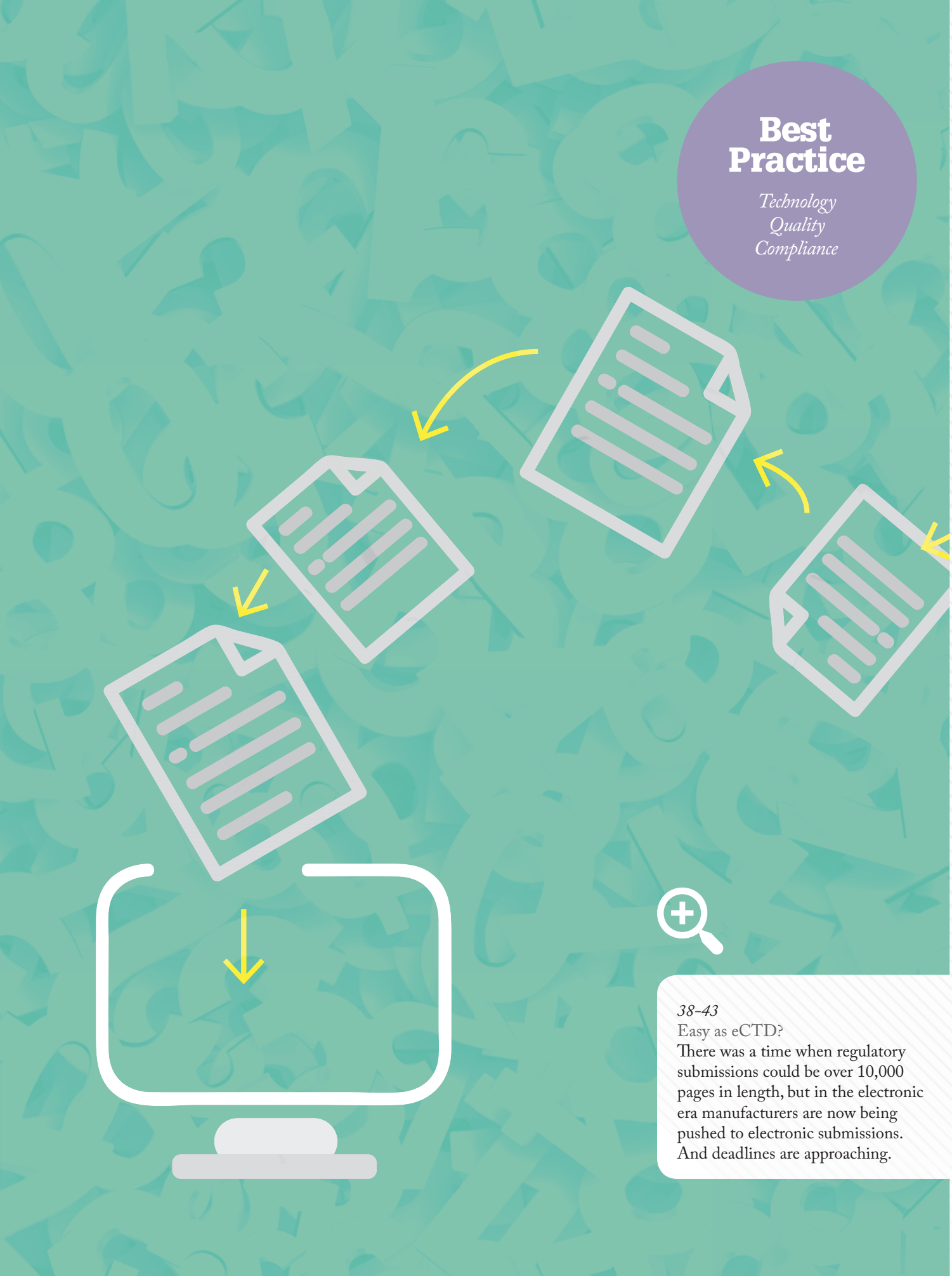
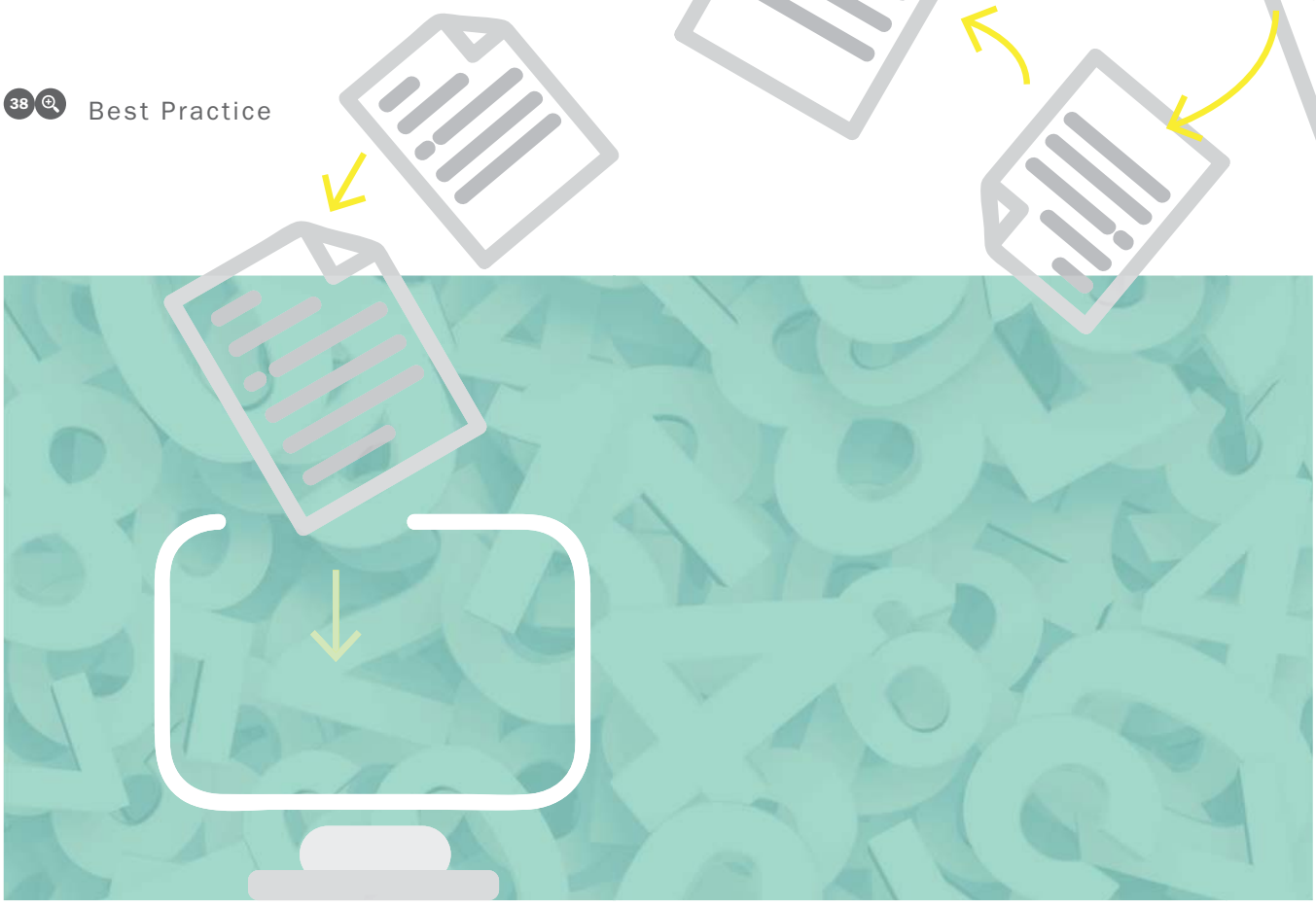


38-43
Easy as eCTD?
There was a time when regulatory submissions could be over 10,000 pages in length, but in the electronic era manufacturers are now being pushed to electronic submissions. And deadlines are approaching.



Easy as eCTD?

Deadlines for mandatory eCTD transitioning are approaching – and companies need to understand how to prepare a compliant submission.

By Pallavi Trivedi

The pharmaceutical market is one with high rewards. It has been reported that pharmaceutical spending growth should match health spending growth at an average of 4.3 percent during 2015-2019, and global pharmaceutical sales should reach $1.4 trillion (€1.18 trillion) by 2019. Biotech drug sales reached an estimated $289 billion (€244 billion) in 2014 and are projected to grow to $445 billion (€375 billion) by 2019. In addition, biotech's share of worldwide prescription drug and over-the-counter sales is projected to increase from 23 percent in 2014 to 26 percent in 2019 (1).

On average, it takes around 12 years for a new drug to go from invention to market. During this time, a tremendous amount of information about the molecule will be collected. If a drug is ultimately successful in clinical studies, the pharma manufacturer will seek regulatory approval via a Marketing Authorization Application (EMA) or New Drug Application (NDA), which should demonstrate the analysis of data obtained during development. These applications are complex, lengthy documents; in the 1990s, a typical MAA consisted of at least 100,000 pages. To standardize the application dossier, the Common Technical Document (CTD) was developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in collaboration with the EMA, FDA and Japanese Ministry of Health, Labor and Welfare.

The CTD describes the organization of modules, sections and documents to be used by an applicant for the marketing authorization of a medicinal product for human use in the three regions that are party to the ICH. Figure 1 demonstrates the five models of CTD: region-specific information, summary documents,

"CTD has revolutionized regulatory submissions… there is no need to reformat the lengthy information for submission to different regulatory authorities."

quality-related information, non-clinical study reports, and clinical study reports. The CTD is defined as an interface for industry-to-agency transfer of regulatory information, while at the same time taking into consideration the facilitation of the creation, review, lifecycle management, and archiving of the submission.

It is fair to say that CTD has revolutionized regulatory submissions – primarily because the standardization means there is no need to reformat the lengthy information for submission to different regulatory authorities. In July 2003, the CTD became the mandatory format for new marketing authorization applications to the EMA and Japanese regulator, the PMDA – and the strongly recommended format of choice for NDAs in the US. But today, we live in the electronic age, so it is only natural for regulatory submissions to move to an electronic format – enter the electronic Common Technical Document (eCTD).

For a number of years now, applicants seeing marketing authorization for a drug product have had the option of submitting an eCTD in parallel with a paper CTD submission, but regulators now want to make most submissions electronic only. Many of the deadlines for moving to electronic submissions have already passed, but others are approaching rapidly.

Embracing the electronic way

In the US, the eCTD is now the standard format for submitting applications, amendments, supplements, and reports to the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research. All submissions must be transferred to eCTD format for investigational New Drug Applications and Drug Master Files from 5 May 2018, and all other applications must be submitted via eCTD or they will not be filed by the national regulators, including FDA or MHRA. For the most part, the US industry has embraced eCTD. Since the introduction of eCTD, submissions to FDA using this format have grown each year. In fiscal 2007, eCTD submissions made up about nine percent of NDAs; in fiscal 2016, eCTDs accounted for 93 percent of NDAs.

In Europe, the picture – and uptake of eCTD – has been somewhat different. Out of 28 National Competent Authorities in Europe, 21 still accept paper submissions for national applications. Although the use of paper submissions is relatively

Benefits of eCTD

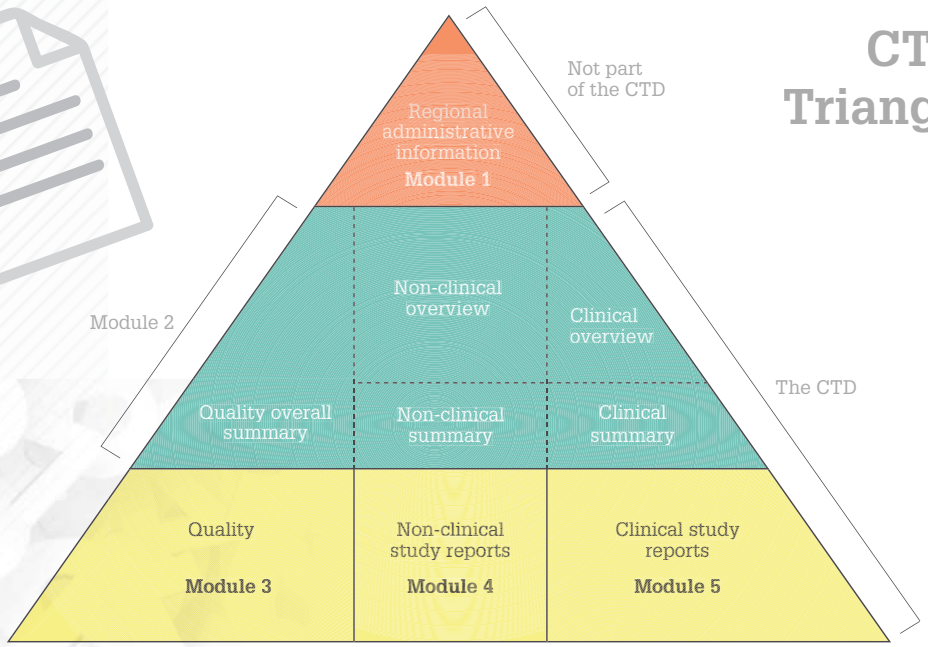
- Improved reviewer efficiency
- Reduced time to approval
- Submission via Electronic Submissions Gateway (ESG) (US) and Common European Submission Platform (CESP) (Europe) enable immediate receipt by the regulatory body
- Improved handling and archiving of submissions (both sponsor and regulatory body)
- Search functionality and increased tracking ability
- Accessibility of documentations across modules
- Ability to re-purpose documents for submission in other regions
- Simplified lifecycle management
- Avoids duplication of the information within the application

rare, some manufacturers use Non-eCTD electronic Submissions (NeeS) or a single pdf-file – neither of which are ICH standard. A number of initiatives have been undertaken to improve electronic submissions within the region. For instance, the EMA has required mandatory eCTD for applications of Centrally Authorized Products for human use from 2010. The agency has also developed structured electronic Application Forms (eAFs) and worked with the Heads of Medicine Agencies to set up a Common European Submission Portal (cesp.hma.eu) to facilitate the move to eCTDs. The initiatives have been developed with the support of the European pharmaceutical industry because of the benefits that standardization and eCTD offer – in particular, eCTDs promote open international standards and interoperable systems that support the exchange of data and documents, thus easing the regulatory process for companies.

"Most European organizations are now well on their way to embracing eCTD – which will ultimately reduce the workload for regulators and help them to function more efficiently."

There was a need for Europe to establish a clear roadmap that would remove the need for paper and physical electronic media to enable the

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

pharmaceutical industry and regulatory authorities to plan for necessary investments and organizational The aim behind this has been to help to improve efficiencies, reduce the administrative load and increase transparency via a more streamlined approach to electronic processing of information. Its intended purpose is also to allow for the availability of all information electronically to both the authorities and industry in a single source.

Mandatory eCTD is required for all new MAAs submitted under the National Procedures (NPs) by July 2018 and for all regulatory activities affecting NPs from January 2019. Final guidance for the initial implementation of the electronic submission requirements includes new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), master files and for commercial investigational new drugs applications (INDs). The schedule indicated that NDAs, BLAs and ANDAs should be submitted electronically in eCTD format starting on May 5, 2017 (May 5, 2018 for commercial INDs) but the submission of master files in eCTD format was extended by one year to May 5, 2018 in response to industry pressures and internal reviews. Exempted submissions only include non-commercial INDs which refer to products that are not intended to be distributed commercially as well as investigator-sponsored INDs and expanded access INDs. However, while these are an exception to the rule, submissions in eCTD are still accepted.

Most European organizations are now well on their way to embracing eCTD – which will ultimately reduce the workload for regulators and help them to function more efficiently. Hopefully, this will result in faster review of submissions and reduced time to market.

Making the move

For companies that have not yet embraced eCTDs, the clock is ticking. Transitioning from NeeS to eCTD submissions requires time and financial investment. And, in my experience, manufacturers should expect preparation

A Smooth Transition

I was recently involved in helping West Pharmaceutical Services make the transition to eCTD. West maintains an extensive Drug Master File (DMF) portfolio with the FDA and Health Canada for its products and processes. The company issues more than 1,500 Letters of Authorization to its customers annually and its elastomer formulations DMF is one of the most heavily accessed master files held by the FDA. Given this, the agency was very amenable to seeing these DMFs transitioned to eCTD, and had discussed the possibility with West on several occasions.

West initially developed a strategy document detailing necessary steps, required deliverables and critical interdependencies before evaluating existing in-house document management platforms and external electronic publishing options. The team then identified additional software requirements to establish a robust electronic submission management system. For document authoring and management, the firm assessed an existing platform to determine whether it could be sufficiently customized to support its requirements, including versioning and document approval for traceability; meeting agency PDF document security specifications; and maintenance of document integrity. West evaluated three options for its electronic publishing needs: software purchase, Software-as-a-Service (SaaS) and outsourcing. Each option was evaluated against the estimated submission workload to compare cost effectiveness. Ultimately, West selected the SaaS option as the best choice based on their need for flexibility and ability to accommodate its specifications.

Without a conversion method for implementing the database solution, West decided to engage both the FDA and Health Canada in a collaborative effort to define best practices moving forward. It was a unique opportunity to build and refine DMF submission requirements and it was in the mutual interest of West, its customers, and the FDA to optimize the submission process.

In the collaborative discussions that followed, West and the FDA identified and addressed challenges in the former process, as well as challenges specific to managing eCTD DMFs in the process moving forward. For example, Letters of Approval (LOAs) have always been processed using paper copies at the FDA and managed separately from the DMFs. However, with the move to eCTD, both West and the FDA will manage LOAs electronically as part of each DMF, which required a new management process.

West submitted five DMFs in eCTD, including four conversions and one new submission. Each DMF can now be submitted to the FDA centers and Health Canada. By using eCTD for the DMF, customer feedback was positive with a direct benefit to their overall submission process, including a simplified, streamlined review experience.

of their first eCTD submission to take between six to 12 months. This transition will require infrastructural changes at an organizational level. One of the main challenges for manufacturers is their own regulatory infrastructure and how submission documents will be processed and archived. Companies also need to choose an electronic publishing option to meet their needs. They must create, authorize and share documents electronically, and must adopt electronic document creation and processing for the information that needs to be submitted in the application.

Setting up an eCTD platform requires not just a change in the document creation and maintenance practice, but also procurement, set up and validation of the eCTD software and other associated tools, such as the validator. Companies also need to be mindful about the compatibility of these software options. These specialized software options require technical expertise to handle and, thus, recruitment of experts and training of users is required. Setting up clear workflows and written procedures is a must to reduce variability between different parties within the company.

"These specialized software options require technical expertise to handle and, thus, recruitment of experts and training of users is required."

Preparation ahead of these deadlines is key as this will position a company well against its competitors. Equally, by having a strong regulatory resource, this will enable the company to grasp a deep understanding of the submission requirements, which will set the foundation for further understanding of the technical skills and regulatory requirements necessary to file compliant eCTD submissions. In addition, readdressing best practices for the use of programs such as MS Word and Adobe Acrobat in preparing content for eCTD will not only ensure increased efficiencies but also reduce the risk of delays for future eCTD filing.

All of this time and effort will ultimately be rewarded; moving to eCTD will ease the regulatory review process, minimize back-and-forth with the agency regarding submission content and quality, and improve the chances of approval during the first review cycle. Whether manufacturers are preparing to transition to eCTD in Europe or the US, the countdown has begun; companies must get to grips with the new requirements.

Pallavi Trivedi is a regulatory consultant at Morningside Healthcare, UK, and an active member of the Regulatory Affairs Professionals Society (RAPS) and the RAPS European Council (REC).

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46–49
Training the Workforce of the Future
Jefferson (Philadelphia University and Thomas Jefferson University) in the US and Ireland's National Institute for Bioprocessing Research and Training have joined forces with a mission in mind – helping to train the next generation of biopharma workers.

Training the Workforce of the Future

Students have access to a vast knowledge base at university, but are they learning the skills required for a career in biopharma manufacturing? Jefferson and NIBRT unite to better equip the workers of tomorrow.

By Kathy Gallagher and Ron Kander, Thomas Jefferson University

In July 2017, Thomas Jefferson University and Philadelphia University merged to create the new "Jefferson." Over the course of the past seven months, we've been asking ourselves some searching questions: what could we be doing differently? Where are the opportunities? What can we achieve together? The first major program to emerge from this creative disruption is a partnership with Irelands' National Institute for Bioprocessing Research and Training (NIBRT). The aim of the collaboration? To establish a Jefferson Institute of Bioprocessing – the first of its kind in North America.

It all started around 18 months ago when Mary Lynne Bercik – who graduated from our business school and now works as a supply chain expert at Johnson & Johnson – heard about the merger. She started thinking about what could be possible with the medical, engineering, and business schools all together at one university. Working for J&J, she knew that biologics had become around 40 percent of the R&D research chain, and that the manufacture of those biologics had been identified as the biggest risk factors in the supply chain. She also knew that J&J and other large pharma companies frequently sent people to NIBRT for training in that area, so she put these factors together and suggested Jefferson look to replicate NIBRT's success in the US.

Naturally, we thought the idea was great! But we didn't want to compete with NIBRT. Instead, we invited NIBRT to partner with us to help deliver the same curriculum at a new institute in Philadelphia. Around 16 months ago, we went to Ireland and we matched up perfectly (both technically and from a personality point of view), which got the ball rolling. We were delighted to make the official announcement of the partnership on February 21, 2018. We are now looking to have our training facility up and running in one year's time, by March 2019. The new institute will focus on three areas:

- Educating graduate and undergraduate students in bioprocess engineering.
- Providing opportunities for industry professionals to come in and conduct workshops and courses – using the exact same curriculum that NIBRT uses. There are around 900-plus pharma related companies in the North East of the US and around 100-plus universities in the region that could send people to be trained.
- Encouraging workforce development in the local community – there are many local college students and even high school level students who will go on to do technician type jobs in biopharma facilities.

In terms of size, NIBRT's facility is around 70,000 square feet, including labs, conference spaces, and so on. Our facility will be physically smaller, but will be located on an innovation campus that already has a conference center and other amenities located within NIBRT. We will exclusively focus on single-use processing technologies, rather than stainless steel, because the bright future of biologics is in modern personalized medicine applications. Applications such as CAR-T cell therapy require the ability to flexibly manufacture small batches of customized pharmaceuticals. And single-use reactor technologies allow for this manufacturing to occur in a rapid, cost-effective manner.

For us, the relationship with NIBRT is part of our larger strategy of building "Jefferson centers" around the globe: we have a Japan center, an Israel center, an Italy center, and now we are working on establishing an Ireland center. The ultimate aim is a state of global synergy in research and focused education-based collaborations.

Hitting the ground running

Our provost, Mark Tykocinski, envisions the new Jefferson University as being the first in a series of new professional "Ivy League" universities. The first part of that concept is about distinction. The second part is about equipping students with the skills and experiences that will allow them to hit the ground running when they enter the workforce.

There's a huge demand for practical skills in the pharma industry – but it's more than just learning how to operate the machinery. It is important to allow students to learn how to coordinate with everyone in the whole production process – scientists, engineers, technicians, and so on. It's important to learn how everyone fits together. When a group of students leave NIBRT, they leave as a team – even if they never see each other again. This philosophy is quite similar to the concept of Nexus – or transdisciplinary – learning, which we've developed at Philadelphia University. And Jefferson's Centre for Inter-professional Education is also known for training all the members of the healthcare team together. This style


nibrt

Training Exemplar

Dominic Carolan, CEO of NIBRT, explains how the collaboration got started – and why

How did the collaboration start?

I was giving a talk at the DCAT conference in New York (on Saint Patrick's Day as it happens) in 2016. Mary Lynne Bercik from J&J was in the audience and liked what she heard, and asked why the US didn't have anything similar to NIBRT. She then initiated conversations with the two universities, Philadelphia and Thomas Jefferson, and a body of interest culminated in a visit to NIBRT. There were a dozen or so representatives from both universities at NIBRT's Biopharma Ambition conference in September 2016. They were enthused by what they saw, and the concept crystalized.

What did they like about NIBRT?

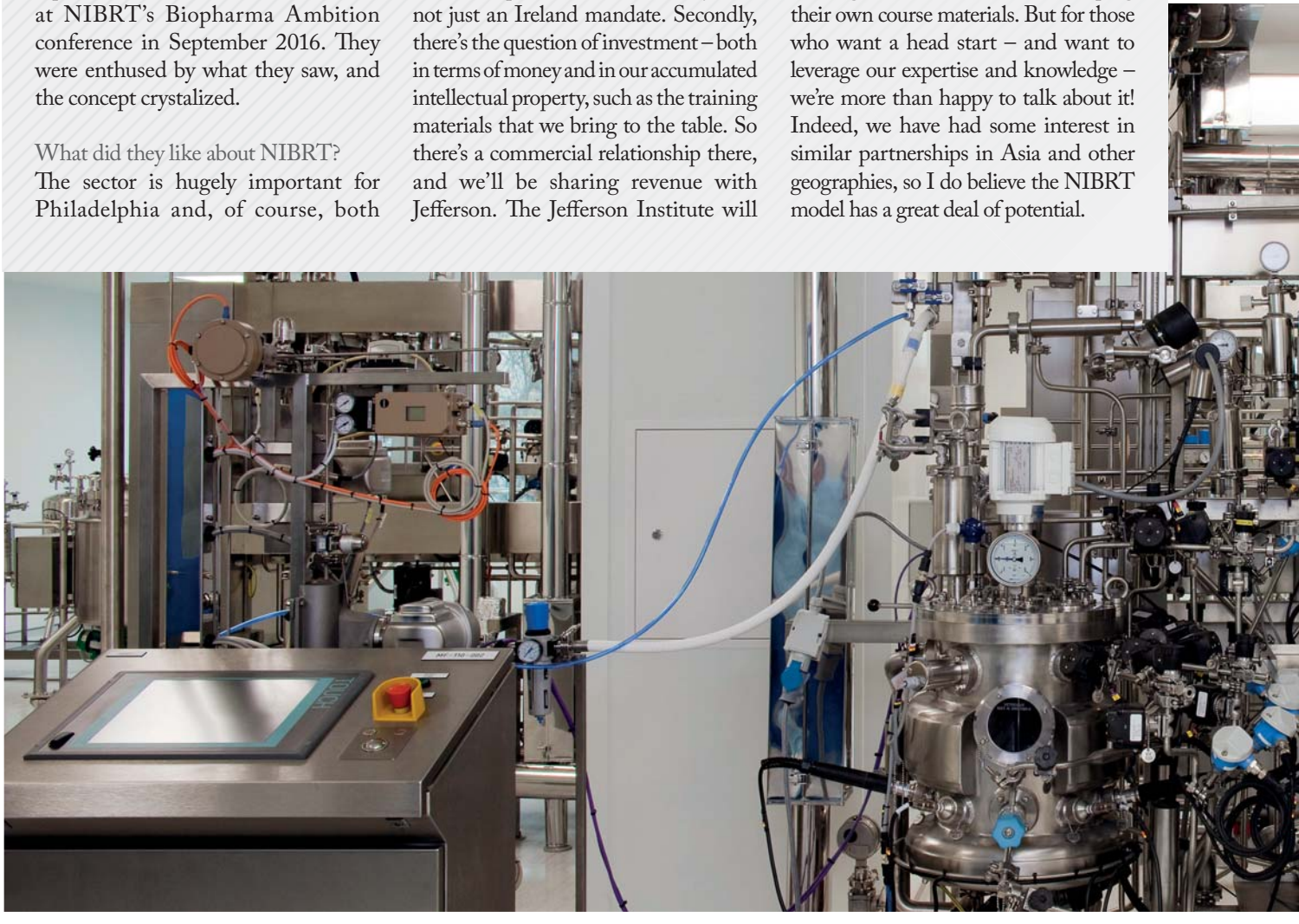
The sector is hugely important for Philadelphia and, of course, both universities were merging into Thomas Jefferson, which meant the institute could work as a potential flagship program. I went over there in 2017 and met the presidents of the universities, both of whom seemed excited about the prospect of working with us. We've been in the business of developing our training curriculum for the past 10 years, so we understand what the industry wants and needs. Many of our clients are US companies, and although we do train some people from the US, it's an expensive proposition to train a significant number of people in Ireland. So the idea was to have a NIBRT-like facility in Philadelphia for North America.

What's in it for NIBRT?

Firstly, we have a global mandate to train and develop talent for the industry – it's not just an Ireland mandate. Secondly, there's the question of investment – both in terms of money and in our accumulated intellectual property, such as the training materials that we bring to the table. So there's a commercial relationship there, and we'll be sharing revenue with Jefferson. The Jefferson Institute will be focused on single-use technologies, in partnership with GE and J&J. We'll facilitate the training of their trainers, using NIBRT's curriculum.

Can you see the NIBRT model taking off elsewhere?

I think the collaboration shows that we're well recognized within the global biopharmaceutical industry. The industry is growing at 10 percent per annum, and the need for talent is huge – and it's rewarding to know that we are looked upon as an exemplar of how to develop talent for the industry. We've had colleagues from a number of other countries – France, Belgium, Denmark, and so on – coming to Ireland to see what we do. Quite a few countries will go off and start their own facilities from scratch, training their own staff and developing their own course materials. But for those who want a head start – and want to leverage our expertise and knowledge – we're more than happy to talk about it! Indeed, we have had some interest in similar partnerships in Asia and other geographies, so I do believe the NIBRT model has a great deal of potential.



of education is clearly very attractive to employers. Companies, especially in the US, are less interested in what you know, and more interested in what you can do. Engineering is a great example. Engineering degrees in the US are all accredited by ABET. If you are a chemical engineer at our university and I look at your transcript, it is going to look pretty much the same as a transcript from any other university – course-wise you will have taken the same modules and gained the same basic knowledge. So how do you separate candidates? Well, practical experience in a facility really makes candidates stand out. Plus, "soft skills" – for example, understanding person-to-person interactions in the work environment – are only going to increase in value, especially as the rise of artificial intelligence means that more technical jobs will be increasingly done by machines.

Style of training aside, the biopharma sector provides great opportunities for graduates. When you leave university you have two strategic directions to choose from: an established industry with a track record or a new emerging field. If you go into a true emerging field, there are all kinds of opportunities for growth, but there is associated risk. If you go with a well-established industry, there may be stability but the growth potential may be limited. Biopharma manufacturing is interesting because it sits within an established industry – pharma – but uses technologies and techniques that are relatively new. And the medicines being produced are truly exciting. In short, young professionals can be at the cutting edge, but in the context of an existing marketplace, which is a really strategic place for a student to be.

Kathy Gallagher is EVP and COO at Thomas Jefferson University, and Ron Kander is Executive Dean of Kanbar College, Thomas Jefferson University, USA.

No Better Time to Be Humble

Sitting Down With... Bruno Sepodes, Professor of Pharmacology and Pharmacotherapy, University of Lisbon, Portugal, and Chair of the EMA Committee of Orphan Medicinal Products (COMP).

How did it all begin?

As a child, you don't really know what you want to do for a career, but you know what you like at school; for me, it was biology and everything related to the human body. I studied pharmacy at university and I became really interested in chemistry and medicine. After moving into toxicology, it wasn't a big leap to enter the regulatory world – after all, knowledge in toxicology and pharmacology is very important from the non-clinical side when it comes to understanding new drugs. I became an assessor for the Portuguese medicine regulator INFARMED and then the magic happened: I ended up connecting myself with EMA. I feel very privileged to not only be doing something that I love, but to be doing it within an international arena.

How did you become active in "regulatory science?"

My interests have naturally shifted from the research setting to regulatory science as I've spent more time in regulatory roles. I am interested in understanding how we better develop and organize regulatory tools for understanding new drugs. I am now quite proactive in this area and I have students pursuing masters and PhDs in regulatory sciences, which I believe is incredibly useful for society because it helps bring better and safer medicines to patients.

What led to your focus on rare diseases?

I became a member of COMP in 2008. From a scientific perspective, the world of rare diseases is very much unknown, with so many questions and so few answers. The quest for knowledge is very rewarding, but the big problem is funding; we need to be able to develop proper products. I fell in love with the orphan regulation because of the way it was creating incentives for development – and so genuinely changing public health and patient lives. Between 2008 and 2012, when I became Chair of COMP, my passion really blossomed. We are seeing products based on science that are coming through the doors of the agency for the first time – they are completely innovative and have the potential to create wonderful drugs that represent the first of a new class. We see them first and give manufacturers the incentives to carry on, which is exciting!

What lessons have you learned working for EMA?

The EMA is a unique place and so eye opening in many aspects! Collaborating with EMA gives you a completely different view to working within a national setting. When you are in an academic setting, you are very focused on the lab. Even when you connect to the clinical side and get involved with translational work, the truth is that patients, patient organizations and even the industry are very far-away players. Moving to the regulatory arena – especially the EMA (the brain of the regulatory world in Europe) – allowed me to really understand patients as stakeholders.

One of the wonderful things about the EMA is the diversity; not only are you able to meet people from all over Europe, but also from all over the world, such as regulators from the US, Canada, Australia, Taiwan, and elsewhere. The diversity has an incredibly positive impact in terms of what you learn and bring home.

You recently received the EURORDIS Rare Disease Leadership Award. How did it feel?

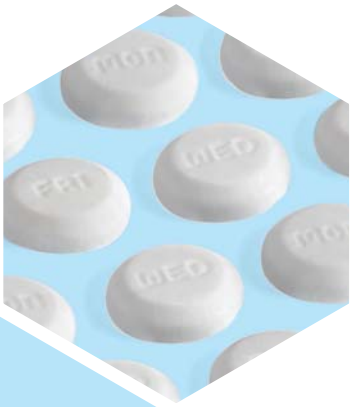
It was very unexpected! I have never felt as if I am doing something that is outside of my job. When I was elected Chair of the COMP, I felt it was my role to not only conduct meetings but also to really get involved with the field of rare diseases and engage patients more in discussions. I can't believe that I been given this award (or that I have been asked to give this interview).

"The quest for knowledge is very rewarding, but the big problem is funding."

I feel very humbled because I have learned so much through the informal interactions that I have had with patients, parents of patients and caregivers. They are unbelievable people – they are fighters and their strength is such an inspiration. I feel very privileged to work in this area and to receive this award – I will treasure it all my life! In today's world, I think it is becoming increasingly rare to receive any sort of recognition and it is very inspiring. My work is just a small part of the overall efforts that have gone into positively changing the landscape for orphan drugs.

Rare Disease Day took place at the end of February. What comes next?

We must not stop the fight! In Europe, regulation around orphan drugs started in 2000. Before then, we had very few treatments for rare diseases and companies were not incentivized to pursue this research. Eighteen years on, and we have made significant progress; there are life-saving drugs available and we have also changed attitudes around rare diseases. I am so happy with the outcomes and I think that all European citizens should feel proud of the accomplishments. We cannot lose this momentum! So many rare diseases still need to be addressed, and there are many other concerns too, such as access to treatment and medicine costs. We need more conversations and we need the participation of every stakeholder. We must not give up because I believe the best outcomes are yet to come.



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