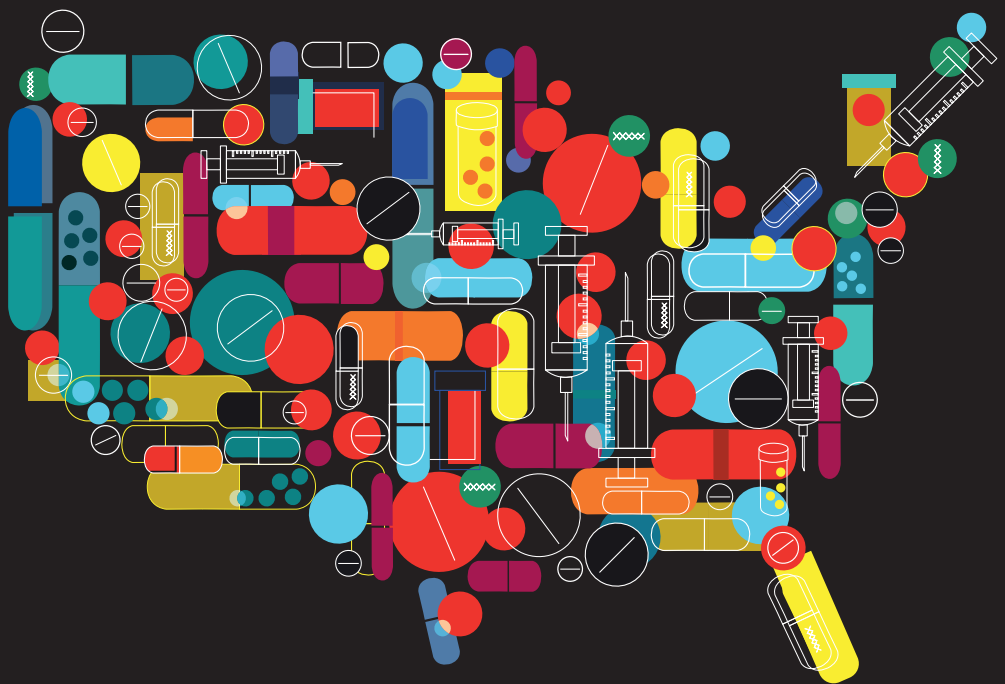
NOVEMBER 2019 # 59

the Medicine Maker™

An All-American Epidemic

The opioid crisis has claimed half a million lives. We examine pharma's role.



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Online this Month

It's in the Water

In the October issue of The Medicine Maker – available at https://themedicinemaker.com/issues/1019 – we examined what actions some pharma companies are taking to reduce their carbon footprints, from harnessing solar energy to power plants, to adopting new waste water treatment strategies. The presence of pharmaceuticals in the water is an oft-discussed topic in environmental circles – but how much of the problem can be attributed to pharma companies? Hector Garcia, Senior Lecturer in Wastewater Treatment Technology at IHE Delft in the Netherlands, gives his view on how we can prevent drug products from entering water supplies.

Available on www.themedicinemaker.com

Solutions in Antibody Drug Conjugates

What are the challenges that CDMOs face when taking on the manufacture of ADCs? We asked John Fowler, Chief Operating Officer, Pharma Solutions at Piramal about the role CDMOs have to play as antibody drug conjugate development becomes more commonplace across the industry.

Available on www.themedicinemaker.com

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the Medicine Maker

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Attack of the Horse Pills

Why are people still being prescribed giant tablets?

Every now and then, the topics I report on as Editor of The Medicine Maker unexpectedly pop up elsewhere in my life. "I'll be back for dinner soon. P.s. I have horse pills!" It was a text from my partner.

I presumed he wasn't speaking literally – it seemed unlikely that he'd somehow acquired a sick horse at work (especially as he is not a large-animal veterinarian). He was on his way home after picking up his prescription and was referring to the size of his tablets. He's never had an issue with swallowing pills before and it's the first time I'd heard him balk at a tablet's size. I inspected the "horse pills" – a commonly prescribed antibiotic for a common infection – and confirmed that they were enormous. But I failed to reassure him about the ease with which he could access their healing powers. "At least they're coated," I said, hopefully.

Earlier this year in The Medicine Maker, we discussed the problems that elderly patients can have in swallowing medicines (1), but the text message from my partner woke me up to the fact that the problem is a broader one. With antibiotics in particular, patient adherence is crucial, so I'm left scratching my head as to why such off-putting tablets have become the norm. My partner will take them (and I will play my role: nagging him to ensure he takes the full course). But how many people out there won't take them or can't take them? Or will just take them until they feel better?

Smarter solid dosage technologies cost more money, but isn't there a better balance to be struck for the benefit of patient compliance? Many big pharma companies have just reported their Q3 revenues from 2019 – and there is plenty of profit to be found. Surely, there's scope to spend a little to make patients' lives easier.

The change doesn't even have to be revolutionary. If ODTs or chewable tablets are out of the question, what about simply creating two smaller tablets instead of one giant pill for larger dosages?

We're just about to enter the third decade of a millenium defined by technological advances – pharma can do better than producing horse pills for humans.

Stephanie Sutton
Editor

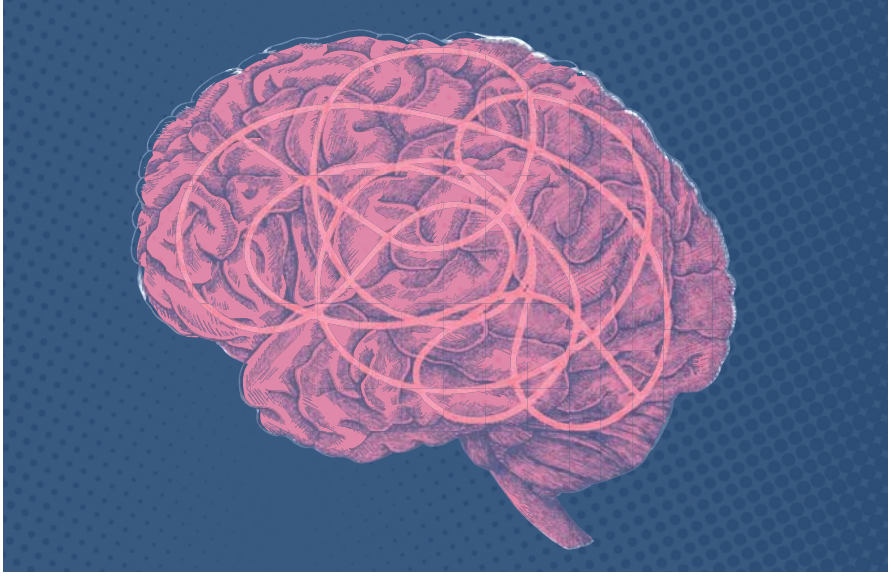
Reference

1. *M Mahdi, S Sutton, "More Than Just a Number," The Medicine Maker, 50, 23-33 (2019).*

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



Beyond the Barrier

Researchers harness bacterial viruses to improve drug delivery to the brain

The blood-brain barrier (BBB) represents a formidable foe for drug delivery scientists, who have experimented with numerous angles of attack. "Over the years, complex design (with poor pharmaceutical attributes), poor target recognition, low frequency of crossing the BBB, and poor ability to subsequently target parenchymal cells (for example, neurons and microglia cells) are among some of the major challenges for achieving drug delivery to the brain," says Moein Moghimi, Professor of Pharmaceutics and Nanomedicine at Newcastle University. Now, a research group led by Moghimi has developed a promising approach inspired by bacteriophages (1).

The team engineered small particles, similar in size to viruses, from peptides that act as drug carriers to the brain. Although Moghimi hypothesized that peptides could be used for the effective delivery of drugs, there were challenges with the design of the peptide – it took his team five years to test the theory.

"Bacteriophages can bind to targets in the brain through display peptides (short peptides in their tails)," says Shadi Farhangrazi, CEO and Co-Founder of S. M. Discovery Group and co-lead author of the paper. "We were able to encourage display peptides to undergo intermolecular interactions and form a hierarchical structure, which helps them to target sites in the brain."

The peptide self-assembles into two distinct self-assemblies, capable of targeting the transferrin receptor (TfR) and the receptor for advanced glycation end products (RAGE) expressed by brain capillary endothelial cells. On passing through the BBB, the peptide navigates its way to the cells that matter (neurons and microglia cells), where it successfully unloads its cargo (2).

The group has already tested the effectiveness of their technology for delivering gene therapies. "We targeted BACE1, an enzyme commonly associated with Alzheimer's disease, using a small interfering RNA (siRNA). We were excited to see that the mice who had received it had lower levels of BACE1 production in their brains," said Farhangrazi. "There was also no evidence of toxicity or inflammation in the mice, which is a positive indication for us that our delivery method could be safe for crossing the BBB in patients."

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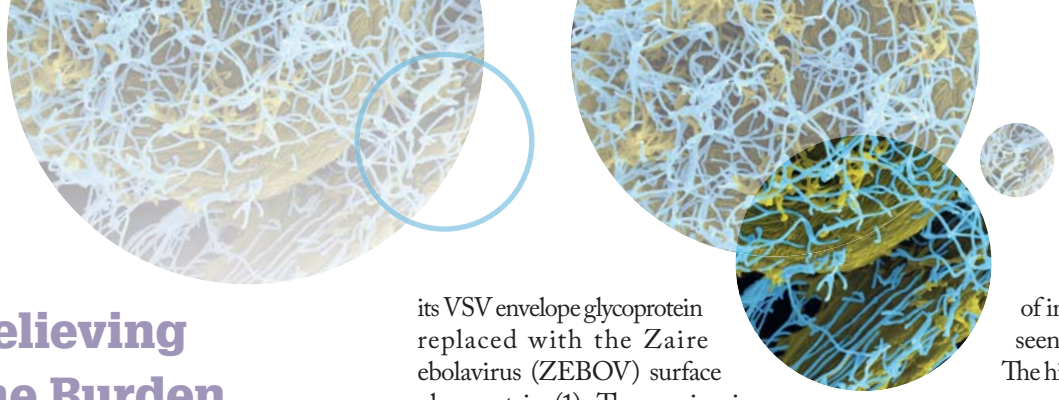
2. *SM Moghimi, "Drug delivery to the brain: self-assembled phage mimetics for crossing the blood-brain-barrier" Available on: https://go.nature.com/2JvdcKQ. Last accessed: October 30, 2019.*



Relieving the Burden

The EMA recommends MSD's Ebola vaccine for approval

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended granting a conditional marketing approval for Merck Sharp & Dohme's Ebola vaccine, Ervebo. According to the EMA, the active substance of Ervebo consists of a live attenuated recombinant Vesicular stomatitis virus (rVSV), which has its VSV envelope glycoprotein replaced with the Zaire ebolavirus (ZEBOV) surface glycoprotein (1). The vaccine is indicated for use in adults aged 18 or over against the Zaire strain of the Ebola virus, which was responsible for the 2014-2016 outbreak in West Africa.

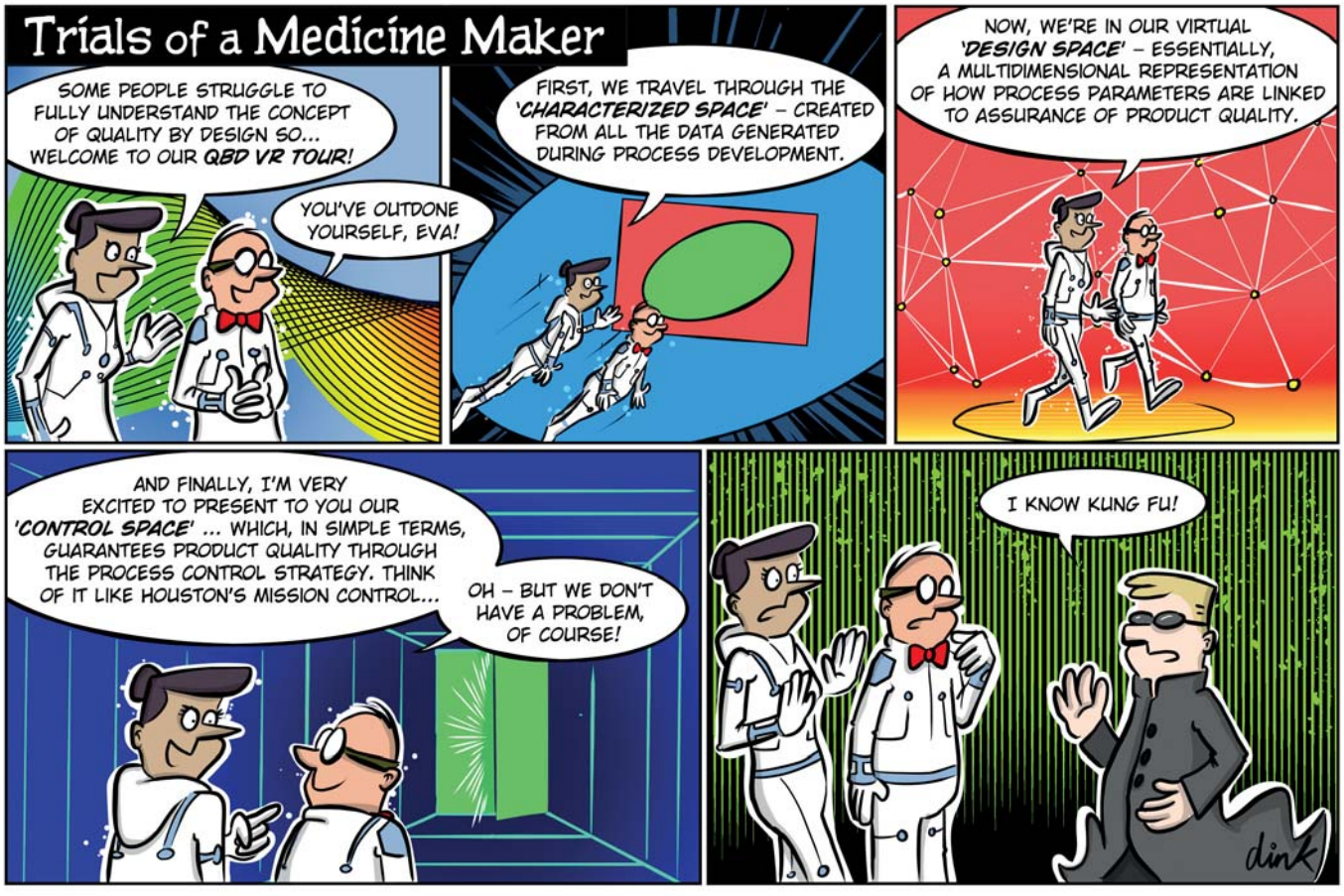
Reviewed under the EMA's accelerated assessment program, Guido Rasi, Executive Director of the EMA, described the vaccine as "an important step towards relieving the burden of this deadly disease." The vaccine has been recommended for a conditional marketing authorization because it fulfills an unmet medical need, and the benefits of immediate availability are seen to outweigh the risks. The highly anticipated approval comes as the crisis rages on in the Democratic Republic of Congo. Since the outbreak began in 2018, 3100 people have been infected with the virus and 2100 have died, according to the WHO.

The drug has also been filed for approval in the US, with a decision from the FDA expected in the spring of 2020.

Reference

1. *EMA, "First vaccine to protect against Ebola," (2019). Available at https://bit.ly/2Ng5KEu. Last accessed October 28, 2019.*

For more adventures featuring Gene and Eva check out our website: themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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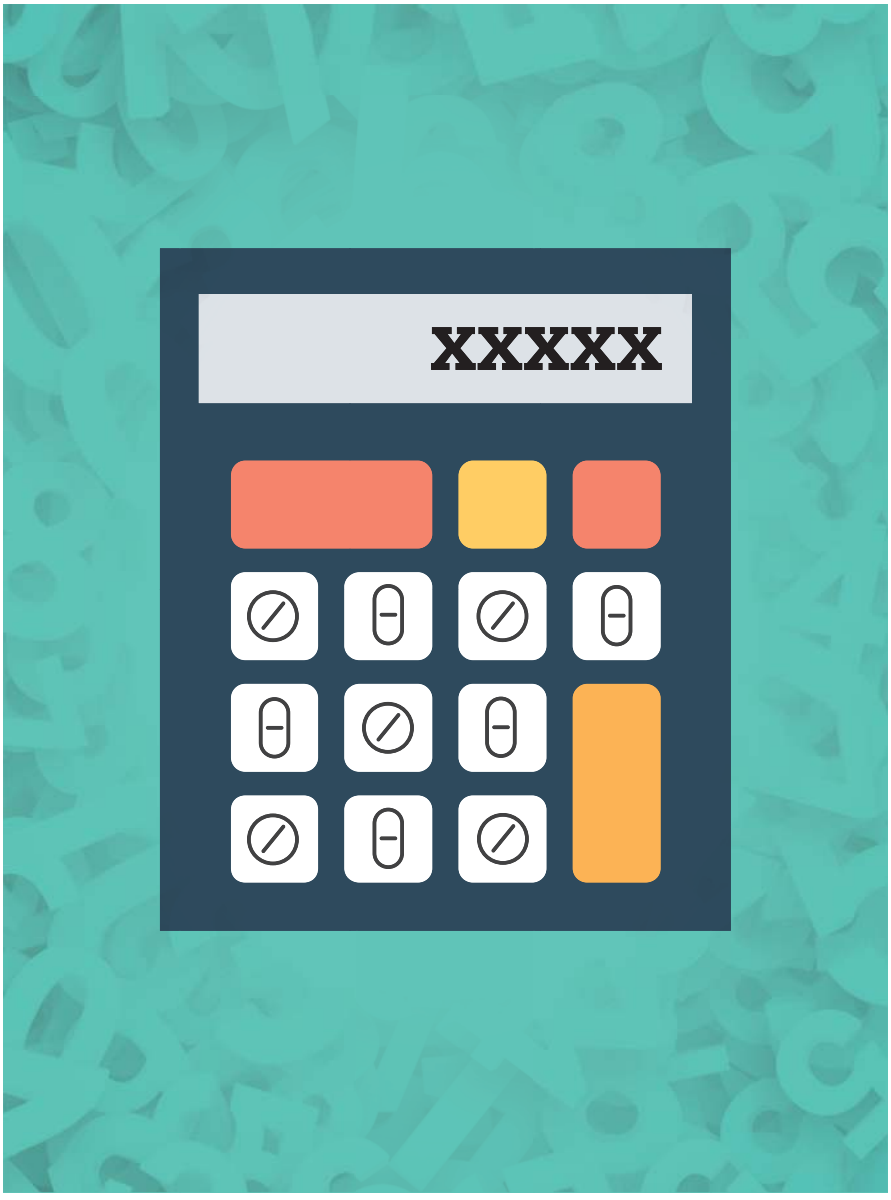
The Risk Calculator

How can we protect patients against drug–drug interactions and adverse drug reactions?



Teaming up with leaders from across the pharmaceutical industry, Elsevier has developed an updated drug–drug interaction risk calculator (DDIRC) to help lower the incidence of adverse drug reactions (ADRs). The DDIRC was developed as part of a two-year collaboration with Boehringer Ingelheim, Eli Lilly, Pierre Fabre, Sanofi, Servier, and several other industry players, to help drug metabolism-pharmacokinetic and clinical pharmacology scientists improve patient safety and outcomes – and reduce risk during pharmaceutical development.

According to Olivier Barberan, Director of Translational Medicine Solutions at Elsevier, drug-drug interactions (DDIs) and ADRs occur at a high frequency, and are increasing as polypharmacy becomes more prevalent. "In Europe, more than 197,000 deaths each year are attributed to ADRs. And in the US, the FDA estimates that more than 106,000 people die every year from these events," Barberan explains. "The DDIRC can be used by drug developers to predict interactions early on, when information on drug candidates is limited, and can also be used in later stages of development."

The phase one version of the new DDIRC is set to be released in early 2020 and will include new workflows, novel ways to visualize data, and the ability to integrate companies' drug and patient data. According to the team, DDIRC improves on the design of current calculators by employing a "mechanistic static" modeling calculator, which establishes the potential for metabolic DDIs between proprietary drugs in development as well as a panel of marketed drugs, using information from scientific literature as well as public regulatory filings from the FDA and EMA.

"The calculator will also be better able to assess the risk of DDI due to polypharmacy, and will deliver accurate, shareable and actionable insights," Barberan said. "Any patient taking more than two drugs is vulnerable, but DDI is particularly prevalent in the elderly and special patient groups like renal- or liver-impaired populations."

DDDIRC 2.0 – the final version of the calculator that will be available in 2021 – will include further improvements and a model for predicting transporter-mediated DDIs.

A Bitter Pill

A new campaign highlights how far businesses have to go to close the gender pay gap – and pharma is no exception

GlaxoSmithKline CEO Emma Walmsley is one of more than 100 high-profile women in the UK to join the #MeToo Pay campaign. The campaign was launched in response to the case of Stacey Macken, a banker who took her employer, BNP Paribas, to court over claims of sex discrimination. Macken, whose annual salary was £120,000, discovered that she was paid £40,000 less than a male colleague in the same role (1).

According to a recent report, 78 percent of companies in the UK have pay gaps in favor of men and the #MeTooPay campaigners have called for "radical and rapid action" to help women in the UK get "the pay they deserve."

Despite being at the helm of one of the UK's largest pharma companies, Walmsley's pay is significantly lower than most of her male peers (2). In 2018, Walmsley made $7.29 million – an increase from 2017, but a long way from the £11.36 million taken home by AstraZeneca CEO Pascal Soriot (3).

In 2017, the UK government made it compulsory for employers with 250 or more employees to publish data about any gender-related discrepancies in pay. Here, we take a look at how salaries compare between men and women at six top pharma companies (AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer and Roche) (4).

Key figures:

- Women earned between 1.3 and 21.3 percent less than men (between 99p and 79p for every £1 earned by a man) – except at Eli Lilly, where women earned £1.01 for every £1 earned by a man (0.9 percent).
- At most companies, women occupied more of the lowest-paying jobs and fewer of the highest-paying jobs. Novartis and Roche were exceptions, with the same or a greater number of women in the top pay quartile.
- Women received smaller bonuses than their male counterparts (up to 38 percent less).

While the figures show a discrepancy in pay in favor of men, the industry is taking steps to close the gap, with companies like Pfizer implementing initiatives to get more women into high-level roles (5).

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Employer	Employer Size (number of employees)	Average difference in hourly pay (%)	Women in lowest paying jobs (%)	Women in highest paying jobs (%)	Women who received bonus pay (%)	Men who received bonus pay (%)	Mean difference in bonus pay (%)	Average difference in bonus pay (%)
AstraZeneca UK Ltd	5000 to 19,999	13.3	51.4	38	86.8	88.7	30.9	25.5
Eli Lilly & Co. Ltd	1000 to 4999	-0.9	45	40	80	73	22.4	22.9
GlaxoSmithKline Services Unlimited	5000 to 19,999	1.3	47.5	41.7	100	100	7.2	-5.6
Novartis Pharmaceuticals UK Ltd	500 to 999	8.4	71	50	95	95	22.5	18.4
Pfizer Ltd	1000 to 4999	21.3	62.5	38	98.5	98.9	40	37.7
Roche Products Ltd	1000 to 4999	9.5	74.7	58	95.7	96	24.1	22.8

Table 1. A comparison of gender-pay discrepancies for financial year 2018-2019

Pure and Stable

Biologics can be finicky when it comes to primary packaging – so it's important to choose wisely

With The Medicine Maker 2019 Innovation Awards just around the corner (check out the winners in our December issue), we caught up with SCHOTT to discuss their syriQ BioPure prefillable glass syringes, which took second prize in our 2018 Innovation Awards. (Catalent's Zydis was awarded first place; read more in the June issue of The Medicine Maker, available at www.themedicinemaker.com).

What key trends in healthcare and the pharma industry influenced development?

There are two key trends that influenced the development of syriQ BioPure: firstly, the growing number of biologics entering the market and, secondly, the need to simplify the administration process for patients through self-administration.

Biologics make up two-thirds of drugs in the development pipeline of pharmaceutical companies and their highly sensitive molecular structure combined with the risk of drug/container interactions requires the drugs to be stored in specific primary packaging that will ensure drug stability throughout the shelf life.

When it comes to self-administration, injection systems need to make the process safe and easy for the patient, who is unlikely to be an expert at administering drugs! For syriQ BioPure, we particularly focused on tight tolerances for a perfect fit and smooth gliding action to ease administration.

When it comes to ensuring drug stability, why is the manufacturing process for primary glass containers or syringes so important?

Though primary packaging containers were formerly seen as a commodity, they are now considered an integral part of the final drug product. Without the right packaging, a drug can neither be transported, stored, nor administered. In other words, getting the packaging right is crucial for a drug's success.

Borosilicate glass tubing is considered the gold standard in the pharmaceutical industry. The manufacturing and converting process of these glass tubes into the primary packaging is a vital step; we've used a specific forming technology to constantly tighten all quality dimensions and increase the overall quality standard of the container. And that results in additional dimensions beyond ISO requirement and tighter geometrical tolerances of the syringes. Moreover, automated inspection systems detect defects that are invisible to the human eye. The goal is to obtain containers with no chips or cracks that feature accurate dimensions and a homogeneous inner surface to withstand drug/container interaction. Our manufacturing process also reduces the amount of tungsten and adhesive residues, as well as particles. And it's validated and documented by the FDA.

How do companies choose which glass they should use?

When deciding on the best material for a specific application, we advise looking at the three "Ps":

- Product. For example, specific requirements the drug might have, such as if it needs a particularly inert packaging.
- Process. For example, how will the product be integrated into existing manufacturing lines or how can it create a low-waste filling process?

- Patient. It is important to continuously meet the patient's needs. Therefore, we evaluate if drug delivery in a home setting is required; if so, the primary packaging must be easy to handle for the patient and work with self-administration devices.

What's next for the product line?
Within the biologic drug market, an estimated 10–15 percent of biologics are ultra-sensitive to silicone. And so we are proud to announce an extension of the syriQ BioPure platform with syriQ BioPure silicone-free. These new syringes avoid siliconization of the syringe barrel while maintaining a consistent gliding force through highly accurate geometry of the container. The new syringes are made of FIOLAX CHR (controlled hydrolytic resistance) glass tubing that – in addition to the certified chemical quality – is 100 percent inspected with our big data process, perfeXion. This syringe is combined with GORE ImproJect Plungers, which eliminate the need for silicone as a lubricant in pre-filled syringes. Designed for use in bare-glass (non-siliconized) barrels, these plungers protect complex or sensitive biologics from silicone-induced aggregation and particulation while maintaining consistent injection performance over time.

Previously, many pharma manufacturers chose to use vials instead of prefilled syringes to avoid silicone contamination, but a silicone-free option will allow a new class of drugs to be manufactured and stored in syringes.

Why did syriQ BioPure rank highly?

Improved drug stability through the use of FIOLAX borosilicate glass under improved processes to lower tungsten and adhesive residuals. High functionality by tightening dimensional tolerances of the syringes beyond ISO requirements to ensure device compatibility by design, as well as a uniform silicone layer for a smooth injection process. Short time to market by providing a full documentation package for the combination product requirements, as well as being able to supply samples within three months to shorten time to market.

Business-in-Brief

Continuous processing, exporting generics and alleviating drug shortages… what's new for pharma in business?

Facilities

- Sanofi has opened a "digital manufacturing" facility in Framingham, Massachusetts, which makes use of intensified, continuous bioprocessing technology, as well as paperless and data-driven manufacturing. The company is also planning to digitally upgrade some of its older plants in Toronto (Canada), Suzano (Brazil), Waterford (Ireland), Sisteron (France), and Geel (Belgium).
- The Shanghai Institute of Pharmaceutical Industry has received an FDA warning letter after refusing a planned inspection. The facility is listed as a contract testing laboratory for API characterization and identification.

Deals

- LIFEPharma has signed an agreement with Apotex, a generic drug producer in Canada, that will enable LIFEPharma to export drugs for commercialization in Canada. LIFEPHarma is based in Dubai and will be the first United Arab Emirates company to export generics to the North American market.
- Back in 2016, the UK's medicines cost watchdog, NICE, rejected the use of Vertex's cystic fibrosis drug, Orkambi, for use in England because of cost effectiveness related to uncertainty around the long-term value and impact. Following over three years of discussions, NHS England and Vertex have finally reached an agreement to make the drug available in the country. Full details of the agreement have not been disclosed, but Vertex will be required to submit its full portfolio to NICE for appraisal.

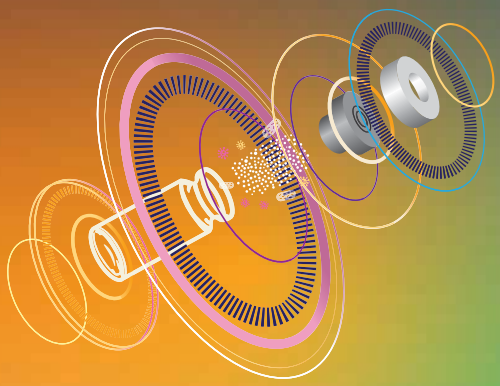
Regulation

- The FDA's Janet Woodcock has recently written a blog for the agency's website urging manufacturers to sell quality to help reduce drug shortages. Although adherence to cGMP is mandatory, Woodcock says that another element to quality in manufacturing is "the ability to reliably make the product in sufficient quantities and with sufficient speed to ensure that supply consistently meets demand over sustained periods of time." The FDA has been exploring a number of potential solutions to drug shortages, including a rating system that could inform purchasers, and even consumers, about the quality management maturity of the facilities making the drugs. The agency is also planning to release a report focusing on the root causes and potential solutions to drug shortages in the near future.

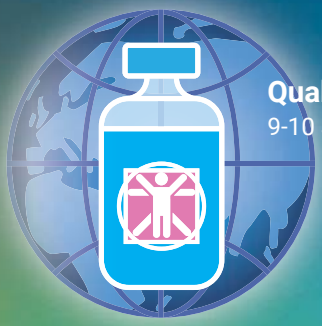
pda.org/global-event-calendar

PDA EUROPE

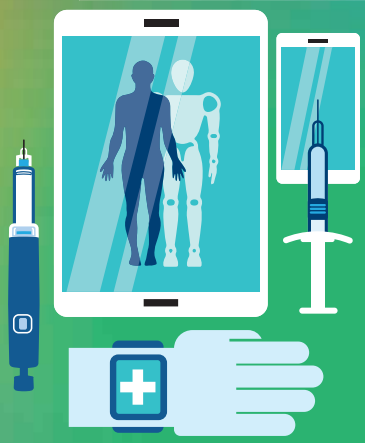
2020 Highlights



Parenteral Packaging
25-26 FEBRUARY



Quality and Regulations
9-10 JUNE



Medical Devices and Digital Healthcare
8-9 SEPTEMBER

Aseptic Animal Health
20-21 OCTOBER

25-26 February	Parenteral Packaging	Basel, Switzerland
21-22 April	Visual Inspection Forum	Berlin, Germany
9-10 June	Quality and Regulations Conference	Dublin, Ireland
22-23 June	Virus Forum	Brussels, Belgium
24-25 June	Advanced Therapy Medicinal Products	Brussels, Belgium
8-9 September	Medical Devices and Digital Healthcare	TBC, Europe
22-23 September	BioManufacturing	TBC, Europe
24 September	Pharmaceutical Freeze Drying Technology	TBC, Europe
20-21 October	Aseptic Animal Health	TBC, Europe

CONNECTING PEOPLE SCIENCE AND REGULATION®

The Human Factor

Single-use systems must be designed with the end-user in mind – because user-friendly technologies help ensure the best product performance, reduce the risk of user error and, ultimately, improve product quality

By Andrew Kit

Figure 1. The Kleenpak® Presto Connector: simple, three-step operation.

The business case for single-use systems (SUS) is becoming ever more compelling with the trend towards flexible manufacturing and the need to get products to market faster. At Pall, we see SUS within our business growing year-on-year as more companies make the switch.

Although the switch from conventional stainless steel to SUS has come a long way, in some cases there is still room for improvement in their design. Good product design must incorporate Quality by Design (QbD) – which ultimately ensures the product is of the right quality at the end of its manufacturing process. In a presentation given by GlaxoSmithKline at the 2019 Disposable Solutions for Global Manufacturing event in Amsterdam, it was said that "QbD is key – no integrity test can replace a bad design."

But a technology is only as good as the effectiveness of the person who uses it. One aspect of product design that is often overlooked is ergonomics and ease of use. It has been said that human error is responsible for more than 80 percent of process deviations in the pharmaceutical and related manufacturing environments (1), and biocontainer/bag leakage is still described as one of the top factors limiting the adoption of single-use technology (2). Reports have shown that improving the reliability of SUS and reducing the risk of leakage requires many actions, including improving the training of end-users and the design of the single-use systems.

In biopharma manufacturing, the design of equipment should help the end-user to operate the technology correctly, which, in turn, will lead to less errors, reduced chances of contamination, and improved product and process performance. SUS design should be intuitive, easy to use, and consistent – and must take into account that there is a human handling the systems and connecting them. This means considering people's mobility, height, strength and reach ranges, for example, during design to ensure that systems are not too complex or too awkward to use. Small adjustments to a product design can go a long way to improving a process; for example, did you know that an uncomplicated task at knee level is much more likely to go wrong than at benchtop? Even simple things like bending down a lot or reaching can also be health and safety issues when added together.

Improving usability

There is a lot that biopharma companies can learn about usability from the consumer world. For example, consider the ubiquitous nature of mobile phones. Fifteen years ago, mobile phones could only be used for calls and text messages, but today you can surf the web, order your shopping, control your heating and more. The ease of using a mobile phone and other devices have changed our expectations of technology and we now also expect other technologies in our lives, from refrigerators to cars, to be easy to use and to incorporate smart technology that enhances the user experience. A good user experience should offer a holistic approach, incorporating both the design of the product and its software. Moving into the pharma and biopharma world, we also expect the same kind of user-friendly technology in our personal lives to be applied to the equipment we use in our professional lives; for example, we expect interfaces and equipment control systems to be intuitive and easy to use and, where appropriate, to be monitored remotely via apps.

At Pall, one of our core values is continuous improvement and we use a kaizen approach to improve our products and services. With SUS, there are some very basic principles that we adopt to enhance the user experience. One example is shadow boarding. This is something commonly used in school classes, such as woodwork rooms, where there might be a board showing the shadow of a hammer or screwdriver. If either of these tools were not in place, the student would know instantly what was missing and where it should go

User-Centered Design

One key tool used in our product design is UX FMEA (user experience failure mode effects analysis). This enables us to benchmark the current end-user workflow and identify opportunities to make improvements through risk mitigation and process improvements. We do this by forming collaborative, diverse and multidisciplined project teams. User-centered design is part of the tool set where the team will:

- *Clearly empathize with the user through:*
  - Interviews
  - Shadowing
  - Observing
  - Research
- *Define who are the people we are designing for:*
  - Creating personas
  - Understanding their objectives, including the pain points and challenges they face
- *Generate ideas:*
  - collaborative, multidiscipline, diverse and inclusive creative sessions
  - develop potential concepts and solutions
- *Prototype early and often to develop meaningful solutions*
  - Build mock ups and prototypes
  - Understand what the final solution could look like
- *Test prototypes with end users*
  - Does the potential solution address the customer and end user pain points?
  - Do users value the potential solution?

once found. It is a simple methodology and it works, so we apply something similar to make SUS installation intuitive. The aim is to ensure that any user can pick up our SUS products and know instantly what to do with it. We also use direct numbering with colour coding on our labelling to help users understand how to install a product. In addition, we have started to embed installation instructions for single-use manifolds on the Allegro™ STR Bioreactor and other hardware user interfaces so the user can look through them at the point of use. This can be useful to verify correct usage, and helps to reinforce training when using the hardware systems.

As one example of how ergonomics can affect product design, consider the Kleenpak Presto sterile connector. When we first started development, we looked at what the users actually needed when it came to connections and worked to understand how they were using current technologies and what the pain points were. We identified error prevention as a very important point – users needed to be sure they had made a successful connection – as well as ease of use, since users would be wearing gloves (sometimes two pairs of gloves are worn in clean rooms) when using the connectors. We also had to be aware of the level of force required to make a connection to ensure that users didn't experience any fatigue or stress in the wrists and the hands. Biopharma manufacturing is repetitive so you need to think of the strain of repeated use. We knew from analysis of competitor products that some connectors required several different actions and a considerable amount of force to actuate.

We addressed all of these considerations and, through iterative testing with end users, came up with a number of solutions. For example, the Kleenpak Presto sterile connector has a strong visual cue if the connection has not been made successfully, as well as a simple "click, pull, twist" three step operation.

Designing for users

When discussing how to improve SUS, the topic of standardization frequently arises. To use an analogy, everyone would like a standard USB connector for everything. But if Pall and all of its competitors started to make the same USB connectors, then end-users would not get the latest innovations, have less flexibility and possibly need to compromise on using the right equipment for the process. We have, however, standardized our range so that once an end-user has brought into a Pall system, they know exactly what they are getting in terms of performance and ease of use. This helps to minimize training because everything is consistent.

Considering human factors in product design can play a huge role in improving efficiency, consistency, productivity and job satisfaction, while minimizing errors. We have been applying this approach for a number of years now and we have a lot of data that helps to drive design decisions. We don't just think, "Users may like X and Y"; we have robust data that tells us exactly what users need, that we have addressed their problems – and ultimately this creates value for end-users because people use the equipment correctly, effectively and safely.

Andrew Kit is Director of User Experience at Pall.

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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

Post-FMD, Post-Problems?

The deadline for the EU's Falsified Medicines Directive has come and gone, but have industry's concerns dissipated? And what new challenges could a no-deal Brexit bring?

By Allan Bowyer, Director of Industry Marketing, at TraceLink

The EU Falsified Medicines Directive (FMD) was published in February 2016. Designed to help protect patients from the threat of falsified medicines, it includes requirements for tamper-evident features and a unique identifier (2D data matrix code) to be added to all medicine packs. The final deadline for drugmakers to comply with EU FMD was February 9, 2019, but have companies met the new demands?

A number of countries implemented post-deadline stabilization periods to help ease the transition and prevent medicine shortages. The approach varies country-to-country, but, broadly speaking, they give dispensers leeway to dispense packs where they are confident an alert is false; conversely, manufacturers are expected to fulfill their obligations to apply the safety features and upload data to the EU Hub. There are a handful of countries that have ended their stabilization periods, while others are beginning to wind down, with most expecting full compliance by February 2020.

It is with good reason that these stabilization periods were granted. The success of FMD – and consequently the security of European supply chains – depends on pharmacists being able to scan and verify every serialized product. But a significant number of hospitals, wholesalers and pharmacies in Europe are still non-compliant. At the FutureLink Barcelona event for example, Emmanouela Nikolakopoulou, Legal Counsel for the European Medicines Verification Organisation (EMVO), stated that over 30,000 community pharmacists, hospitals and dispensing doctors across the EU hadn't connected with their respective national European Medicines Verification Systems. The

"In France alone, only two out of 20,000 pharmacies had established a connection as of early October."

EMVO's weekly monitoring reports show that in France alone, only two out of 20,000 pharmacies had established a connection as of early October, while in the UK, 19 percent of pharmacies and 58 percent of wholesalers were yet to connect with Brexit hampering investment desire (1).

There have also been growing pains relating to data integrity. Initially, handling falsified medicine alerts was a significant concern, with users saying they had not anticipated having to deal with so many so soon. Fortunately, a large portion of these were due to data entry problems rather than malfeasance - and this has mostly been resolved as manufacturers have gotten to grips with serialization in a live environment. There are still a notable number of false alerts occurring but these are largely down to errors made by dispensers (often caused by misconfigured scanners and double scanning/decommissioning). The EMVO has tasked manufacturers with identifying the routes of alerts and reducing the alert rate from its current rate (latest according to EMVO is 2.87 percent) to less than 0.05 percent.

The pharmaceutical industry often faces criticism for being slow to change, and the move away from traditional supply chain systems is still encountering resistance. To bring about real change, greater agility and integration are required in software systems used to manage the supply chain. Whether the user works in a hospital, pharmacy or manufacturing facility, currently available digital systems should facilitate a change in mindset throughout the supply chain.

Now more than ever before, the industry is driven by companies that are producing highly complex, niche products that require adherence to specialized distribution and dispensing models. This makes the end-to-end visibility of the pharmaceutical supply chain imperative, but at the moment, transparency remains a major roadblock. The industry is making progress as companies switch to more appropriate digital tracking systems, but any interruption to the smooth transport of medicinal products within Europe could be a stumbling block. What then, could be the impact of a no-deal Brexit?

"Handling falsified medicine alerts was a significant concern, with users saying they had not anticipated having to deal with so many so soon."

The more boundaries that are put up, the more difficult distribution becomes. How will companies effectively share data between continental Europe and the UK? We believe software as a service (SaaS) platforms could help to manage some of the fallout. SaaS is designed to share relevant data with multiple customers and clients across the pharma industry. Country-compliant modules can easily be added to the platform, so whether a client is dealing with the regulatory environment of the UK, the EU, or even Russia or Saudia Arabia, connections are codified and collaboration and data sharing become less challenging. A pharmaceutical manufacturer in country A will, therefore, be able to effectively establish communication with a retailer in country B once a connection protocol is put in place through the platform.

Despite the well-publicized rumblings around the pharma industry and Brexit, the pharmaceutical industry is one of the best prepared. Unless specifically revoked in a withdrawal agreement, the FMD will remain in place until the end of the transition period – the end of 2020.

If there is no-deal, the EMVO and the UK's national MVO have proposed that the system be kept live for a number of months over a winding down period after the Brexit deadline. Beyond that, there is no legal authority or funding to keep the system online beyond the end of 2019. This will mean that dispensers in the UK won't have to decommission packs, and products destined for the UK from the EU will need to be decommissioned as an export. Most manufacturers operating in the UK, however, distribute products in Europe and will continue to serialize packs accordingly.

One thing is certain: patients everywhere should have access to high-quality medicines without the risk of consuming a contaminated or counterfeit product. The right digital solutions can certainly help to manage serialization and track and trace requirements in a fragmented supply chain in different countries. To keep patients safe in the face of ever-more-sophisticated counterfeiting operations, companies should not settle for compliance with the FMD – they should strive to do better.

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Leading by Example

Brexit is a serious challenge for UK businesses trading with the EU – but there are a number of actions companies can take to mitigate the risk to supply chains

By Nik Kotecha, Chief Executive of Morningside Pharmaceuticals Ltd, Department for International Trade (DIT) Export Champion and a CBI Regional Councillor, UK

Preparing to leave the European Union is one of the most challenging issues facing UK companies today – for many businesses, it will be their number one priority in the months to come. However, there is little certainty regarding what the actual terms of the UK's departure from the EU will be (if indeed there are any), nor when the UK will leave.

My company, Morningside Pharmaceuticals – a manufacturer and supplier of medicines to the UK and international markets – has taken a number of steps to ensure the business is ready for every eventuality. I hope our example may be of use to other UK companies navigating Brexit's murky waters.

To ensure a continuous supply of our medicines, we have taken advice from the UK's Department of Health and Social Care (DHSC) and stockpiled a minimum of six weeks' worth of drugs, to cover any shipping delays at ports caused by a no-deal Brexit. We have also almost doubled our stock levels since December 2018, which has meant finding extra storage space that provides temperature and humidity control. A large number of manufacturers and suppliers are doing the same, which has meant the costs of storage have increased.

When it comes to importing, it's likely that a no-deal Brexit would cause delays at the border, as the free movement of goods ends and goods become subject to customs checks and procedures. The government has stepped up efforts to ensure businesses are ready to trade post-Brexit by automatically allocating more than 88,000 VAT registered companies across the UK with Economic Operator Registration and Identification (EORI) numbers (1), which must start with GB (2). You can also use the Common Transit Convention (CTC) to move your goods more quickly so that customs declarations are not required at each border crossing (3).

As an interim measure, the government is also rolling out Transitional Simplified Procedures (TSP), which make it easier to import goods from the EU in a no-deal situation by delaying declarations and the payment of any relevant import duties and/or VAT. This is something we have signed up to as part of our contingency planning. I would advise looking into setting up a Duty Deferment Account too, which will enable you to make a single customs duties payment per month instead of paying for individual shipments. You must set one up if you plan to use Transitional Simplified Procedures (4). You will also need to check the rate of tax and duty to pay, as you will need to pay customs duties and VAT on all imports (5).

For exporting, a customs declaration will be required for all EU shipments. The rule for pharmaceuticals entering the EU is that any product that is being used in the EU and going to an end patient there, has to be released by a qualified person (QP) within the EU. In the event of a no-deal Brexit, we have made contingency plans to release batches for our customers in the EU. Having an office in the EU will also be vital for preparing for regulatory

"When it comes to importing, it's likely that a no-deal Brexit would cause delays at the border, as the free movement of goods ends and goods become subject to customs checks and procedures."

"We have also almost doubled our stock levels since December 2018, which has meant finding extra storage space that provides temperature and humidity control."

changes brought about by a no-deal Brexit. In particular, having an EU base will enable us to comply with EU regulations around pharmacovigilance. It also means that license for a medicine in the EU must be held in an EU territory.

Other export advice from the government includes: making sure your business has an EU EORI number that starts with GB, checking your importer has an EU EORI number, checking the rate of tax and duty for your goods and checking what you need to do for the type of goods you export (6).

Supply chain holdups, particularly at the Port of Dover, where the majority of goods come across from the EU, is a concern for many businesses. To help alleviate delays at Dover, the government plans to bring in new measures that will improve Kent's resilience if services across the English Channel are disrupted. This is called Operation Brock (7).

To ensure delays are kept to a minimum, the government is running a number of schemes to secure ferry space. They plan to buy space with the ferry operators, which will give businesses like ours the opportunity to register for space and use it for priority orders. The government is also introducing an "Express Freight Service", which will be rolled out if there are any shortages of essential goods, such as medicines. This will see a courier service contracted out to guarantee priority orders have minimal delays.

A facility in the port of Ostend, in Belgium, has been set up too, so if there is a problem, manufacturers can apply for a coupon to move stocks through there efficiently in the event of a no-deal Brexit. Our haulage providers are also taking part in alternative routing, which will look into alternative routes to avoid delays at Dover and Calais.

We are also applying to be an Authorized Economic Operator (AEO) – an accreditation given by HMRC, which shows that our supply chain is safe and secure. To achieve this, a business must submit an application to HMRC, followed by an audit of their supply chain (8). To help prepare for the audit, we carried out a gap analysis to further improve our processes. During this audit, our procedures were reviewed in line with the criteria, which identified any gaps.

Companies can also apply for a Training Grant, which is for any company that has to do additional work with regards to customs procedures because of Brexit. This grant will be paid by the government to the company applying, which will then be able to fund the training from their supplying partner (9).

In short, Brexit creates a number of challenges for UK businesses, but with careful contingency planning – including an exploration of the various government-run schemes available – there are ways to mitigate the risk.

More information, including links to the Government's online advice, can be found in the online version of this article available at www.themedicinemaker.com.

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Getting Ahead of the Game in Cell and Gene Therapy

Successes in the clinic have placed many cell and gene therapies on an accelerated route to market. But unless developers consider, at an early stage, how they might produce their product at scale, they may run into problems with commercial manufacturing. Here, we present an article based on an interview with Carol Knevelman (Vice President, Head of Process R&D at Oxford Biomedica), who shared a case study on large scale lentiviral vector production at GE Healthcare's "Bioprocess Days" event in May, 2019. Carol offers her advice for developing a futureproof commercial process.

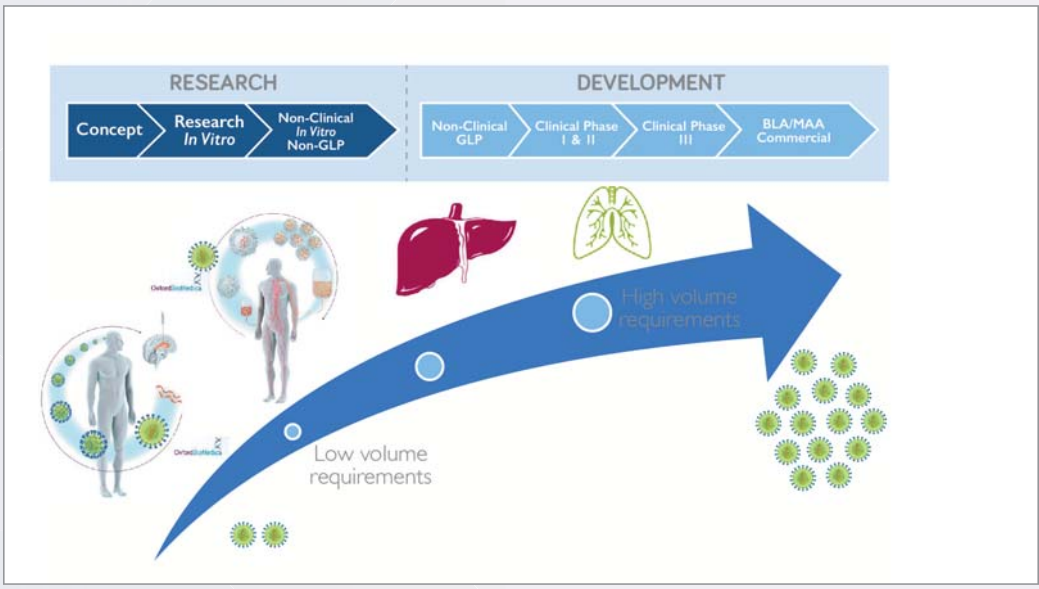


Figure 1: Typical manufacturing strategy considerations.

Many cell and gene therapies are on an accelerated route to market – sometimes skipping phase III trials entirely. With early stage development so close to commercial launch, there's little time to develop an appropriate manufacturing process for commercial supply. This can leave the commercial process looking rather different in terms of production modes and impurity profiles compared to the initial process, and this may necessitate lengthy bridging studies. Because of the fast track nature of these therapies, process knowledge can also be lacking, which can result in extended process characterization studies. All of these factors can delay time to market. Another problem is that the differences between European and American regulatory frameworks can be difficult to navigate.

In the current landscape, most of these therapies come from an academic research environment where, at the preclinical stage, many of the materials used are marked for research only, and are often undefined and uncontrolled. At the clinical stage, these materials must be replaced with GMP-grade materials where it can be difficult to find alternative suppliers or certified materials with equivalent properties. As you transition to GMP-grade materials, the risk associated with the process will decrease, but this will come with greater costs – especially with cell and gene therapies, where products can be priced at $0.5 million to $2.2 million per treatment. We found the complexity of the supply chain for our initial adherent process to be particularly challenging when moving into the clinical arena. Oxford Biomedica had 54 global suppliers for over 400 different components with this process – operating at varying temperatures. There were over 1000 line items required for each batch, which, as you can imagine, created considerable risk. This was considerably streamlined prior to process performance qualification.

Building a vector

Given the myriad challenges, how did we develop a workable manufacturing plan for a commercial process? Speaking from our experience in developing lentiviral vectors for cell and gene therapies, as well as working with companies to apply our technologies to their manufacturing processes, the first step to success involves understanding what is required for your therapy to succeed. For example, the therapeutic area will influence the amount of vector that needs to be made; programs that deliver therapies directly to the brain will have vastly lower volume requirements compared to therapies delivered to organs such as the liver or lungs.

Investing early to get ahead of future demands is also important. For our process, we invested early in suspension cell culture, which is serum and animal component free. Suspension processes can be scaled up relatively easily and can operate in fed-batch or perfusion mode to deliver productivity gains. But there were still many challenges. Vectors are incredibly fussy and sensitive to almost anything that is required for

Enabling Technologies

With Lorenz Mayr, Chief Technology Officer, and Catarina Flyborg, General Manager for Cell & Gene Therapy, both at GE Healthcare Life Sciences

How can the gene therapy sector realize its potential?

Mayr: There is a great deal of discussion in the cell and gene therapy industry about the costs of these therapies. Pricing and reimbursement strategies are, of course, important, but developing enabling technologies to revolutionize how these therapies are produced will be vital to reducing production costs and, ultimately, prices for patients.

I believe that automation and digitalization is key to industrializing these products and unlocking the tremendous potential of the sector. Gene therapies are very specific, bespoke products, but we must find a way of effectively scaling out and making them available to a wide range of people. At GE, we believe biology and technology is converging and this is what we as a company in the biopharma space are particularly good at.

Flyborg: I agree with Lorenz, industrialization will be key. The big challenge moving forward is developing closed, automated and digitalized manufacturing platforms. But, as Carol has laid out, gene therapy developers must be thinking about these things much earlier in development – even at the preclinical stage. And when it comes to digitalization, we need solutions that both monitor and allow us to improve processes through analytics. There is also the possibility of using technology to select the right patients based on how they may respond to a given treatment.

successful manufacture in suspension: pH, temperature, shear forces and so on. Removing impurities within the product stream is also difficult because of salt sensitivity, the mixture of host-cell protein and DNA, plasmid DNA, as well as empty, inactive vectors that can't transduce your target cells.

The solution was to select appropriate scaled-down models for process development. This was crucial given that development at the larger scales would be very expensive with our process! These scaled-down models allowed us to identify the optimum physio-chemical environment within our bioreactors. We were also able to identify initial critical process parameters, as well as much of the necessary engineering characterization to define the scaling criteria required to move forward. Once we had this knowledge, we were able to then identify GMP systems on the market that could satisfy our requirements – in our case, these were all single-use. The preparatory work allowed us to cut costs by minimizing the number of the scale-up evaluations that are typically needed – which is also beneficial because it can reduce overall development timelines and enable faster market access.

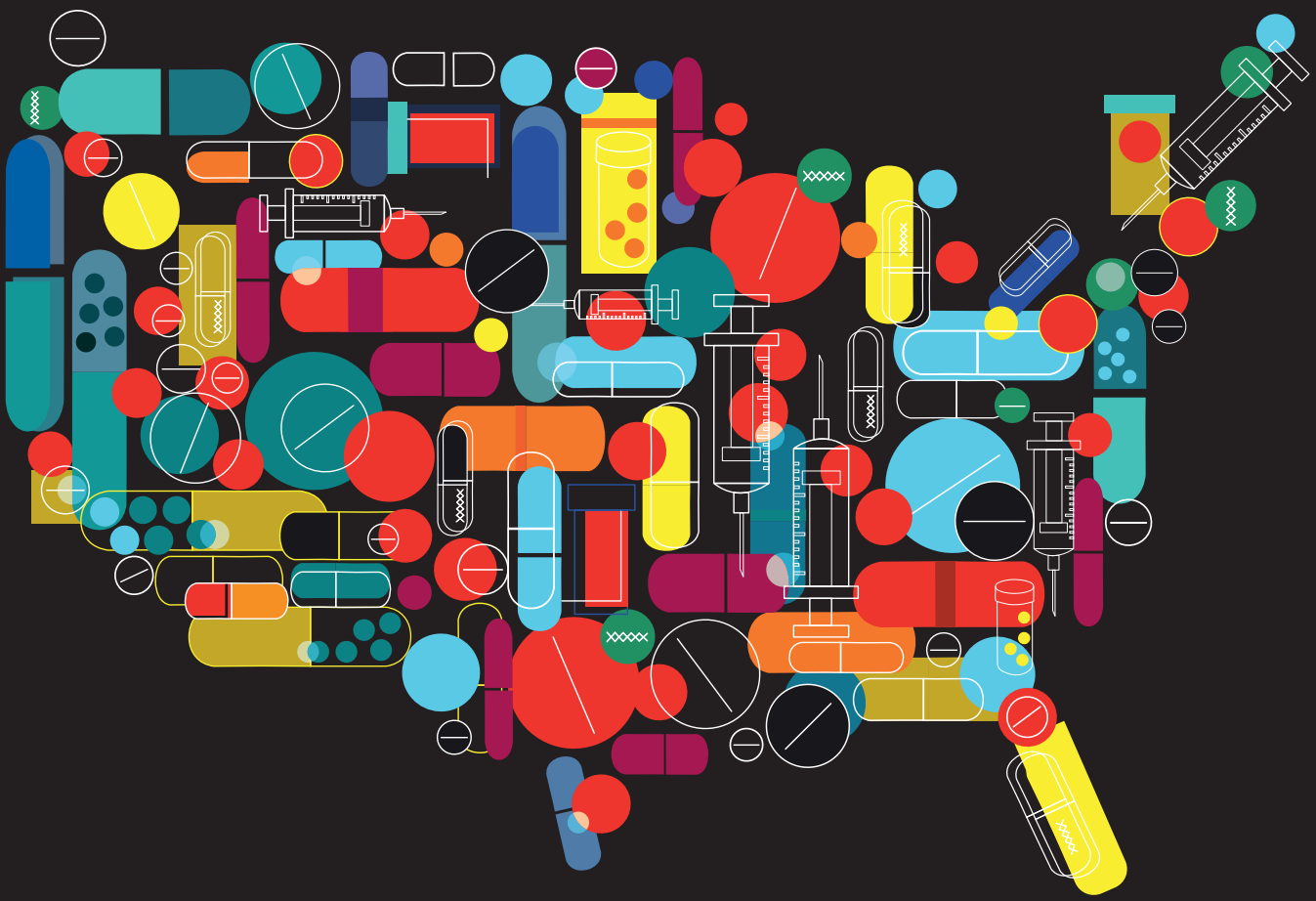
Future challenges

Although the majority of development work was performed in the scaled down models, there were some elements that required evaluation at larger scales. For example, in transitioning from an adherent process to a suspension process, we saw an iterative improvement in upstream titers by a factor of 10 to 20 fold, plus the three fold increase in scale. The increased titers, however, did not initially fully translate from our 5 L scale down bioreactors to our larger scale bioreactors. However, after identifying where the problems were with additional process development, we were able to achieve the same titers in our 50 L and 200 L bioreactors as in our scale down models.

This is sufficient for many of the vector quantities that are required by our partners and should see them through commercial supply for their therapies. But it's still not enough for some indications we're working with, so we will continue to innovate to ensure that we're able to deliver sufficient vector for all indications One such innovation is in an automated cell screening system we have invested in to speed up the selection of cell lines for our packaging and producer cells.

Demand for vector product will only increase throughout the industry as it matures. Indeed, there is already a shortage of vectors as current technologies struggle to keep pace with the expansion of gene therapies from ultra-rare to larger indications. I believe that the success of the industry hinges, in part, on further innovation in vector production platforms and vector purification, in particular. Vendors must continue to improve the scalability and availability of their systems. Here, much can be leveraged from the pharma industry.

I envisage the cell and gene therapy industry transitioning to more intensified processes through integrated continuous processing, automation and digitalization for data management, and single-use systems to improve speed to market. These provide opportunities for achieving cost-efficient, large-scale vector production and achieving the right quality to meet patient needs.



THE (HUMAN) COST OF GREED

To what extent is the pharmaceutical industry responsible for the USA opioid crisis – and the half a million lives lost over the past three decades?

By James Strachan

The opioid crisis in the USA has claimed well over half a million lives – more than the number of American soldiers killed in World War II. At its worst, the opioid crisis claimed more lives in a single year than the number of Americans killed during the entire Vietnam war. The scale of the crisis partially explains why average life expectancy in America declined in 2017 – a first for the developed world.

Issues of prescribing, dependence and misuse are complex and overlapping. When taken for a short time and as prescribed by a healthcare provider, opioids are generally safe: many Americans suffering with chronic pain take opioids for much-needed relief without misusing the drugs – indeed they are the majority (1). But opiates can cause changes in neurological pathways in just a few days, and many abuse the medicines they are prescribed by taking too much – in some cases, crushing pills to either inhale or inject the drug instead – or by seeking early repeat prescriptions. Others may become dependent on illicit drugs and then seek to replace them with prescribed medicines; while others may become dependent on prescribed medicines and then, when they are no longer accessible, seek alternatives from other sources (2).

Tragically, a sufficiently high dose can slow or stop a person's breathing, which can result in death. No one knows the true number of deaths caused by prescription opioids, including diverted prescriptions or counterfeit medicines that have been imported illegally from other countries; toxicology testing cannot distinguish between some pharmaceutically- and illicitly-manufactured opioids, such as fentanyl. Furthermore, drugs are not specified on the death certificate in approximately 20 percent of overdose deaths. And in 2014, multiple drugs were involved in almost half of the drug overdose deaths that mentioned at least one specific drug on the death certificate (3).

But we do know that more than 50 percent of overdose deaths during the course of the USA opioid crisis were related to prescription opioids. Regardless of how they are taken, these are drugs manufactured by pharmaceutical companies, approved and licensed by regulatory authorities, distributed by wholesalers, and prescribed by medical professionals. And that raises some big questions. How could such harm come from legitimate attempts to treat pain? Why couldn't the authorities prevent misuse? Will bad actors be brought to justice? What should be done to halt the situation and ensure it never happens again?

THE ORIGIN STORY: LEGITIMIZING OPIOIDS FOR CHRONIC PAIN

The global medical community was for a long time cautious about prescribing opioids to treat pain. As Marcia Meldrum notes in an article for the American Journal of Public Health, back in the 1970s, "Physicians and nurses were trained to give minimal opioids for pain, often even less than prescribed, unless death seemed imminent. Chronic pain, a few studies noted, was badly undertreated," (4). But in the 1980s, the consensus began to shift as a group of pain specialists advocated for better pain management – particularly in cancer patients.

"There was an earlier pendulum swing," says Tom Frieden, former director of the US Centers for Disease Control and Prevention, and President and CEO of Resolve to Save Lives, an initiative of Vital Strategies. "From after the Civil War until around the 1920s, opioids were widely used, resulted in lots of addiction, and then there was backlash which led, often, to an undertreatment of even severe acute pain over the course of several decades," he says.

Authur Gale, who practiced internal medicine during the 1970s, believes the US opioid crisis began – insofar as the role of medicine is concerned – with an obscure US Supreme Court decision known as "Goldfarb" in 1975. "This decision determined that medicine (and law) were no longer to be considered professions, but were, in the words of the court, 'ordinary purveyors of commerce,'" he says. "Before Goldfarb, physicians were very careful about prescribing opioids."

In 1980, Jane Porter and Hershel Jick wrote a short letter to the editor in the New England Journal of Medicine describing their analysis of 11,882 patients who received narcotics in a hospital. They found that there was only one "major" instance of addiction. The letter became a prominent resource of pain-relief advocates and has been cited more than 900 times (5), despite being only five sentences long.

In an interview for the book "Dreamland: The True Tale of America's Opioid Epidemic" Marsha Stanton, a nurse, told the author that she and other seminar speakers often cited it during the 1990s. "We all thought it was gospel," she said (5).

But the original analysis wasn't a peer-reviewed study – and nor did it look at those patients taking opioids for chronic pain outside of a hospital setting. And in 2017, a bibliometric analysis of the letter (6) found that it was "heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy." The authors concluded, "This citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy."

"More than 5000 physicians, pharmacists, and nurses attended these all-expenses-paid symposia, where they were recruited and trained for Purdue's national speaker bureau."

Nevertheless, the letter became part of a body of evidence that contributed to changing opinions on opioid therapy for chronic pain, which included two highly influential articles published by Kathleen Foley in 1981 and 1986, reporting on the low incidence of addictive behavior in small groups of cancer and noncancer patients (4). Russell Portenoy had been working under the supervision of Foley and became a vocal advocate for the use of opioids to treat chronic pain – giving talks at conferences and seminars, as well as writing numerous articles and book chapters on pain.

The WHO published new guidelines for treating cancer pain in 1986 – recommending the use of strong opioids in cases of persistent pain after treatment with non- and weak opioids. As prescribing trends matched the new guidelines, a number of publications began to question why opioids were reserved solely for cancer pain (7), including an article in Scientific American titled "The Tragedy of Needless Pain," which described Jick and Porter's five-sentence letter to the editor as an "extensive study."

According to Marcia Meldrum, the best-known alternative to opioids is a "multidisciplinary team approach involving reliance on physical and psychological therapies, including cognitive-behavioral therapy, relaxation and pain-coping skills training, and self-hypnosis," (4). But such methods are poorly covered by insurance providers in the US. And throughout the 1990s, opioid therapy gained support from experts, government agencies, and national nonprofits. And that opened the door for opioid manufacturers.

MARKETING OPIOID THERAPIES

Opioids have been commercially produced since the early 19th century and there were a number of brand name and generics opioids available in the 1980s and early 1990s. But these products only provided short-term pain relief – up to six hours.

Purdue Pharma developed a morphine formulation that could relieve pain for between eight and 12 hours that went off patent in the late 1980s. To avoid generic competition, the company developed an extended release formulation that they claimed would be effective for up to 12 hours: Oxycontin.

Oxycontin was approved by the FDA for moderate-to-severe pain, when an around-the-clock analgesic is needed for an extended period of time. A key decision in the opioid crisis timeline was the FDA's decision to allow Purdue to claim, on the original label, "Delayed absorption as provided by Oxycontin tablets, is believed to reduce the abuse liability of a drug." This sentence would form the basis of the company's marketing campaign and remained on Oxycontin's label for more than five years before the FDA removed it and added a "boxed warning" on the label to signify the drug's serious or life-threatening risks (8).

Purdue spent over $200 million on Oxycontin marketing in 2001 alone. Art Van Zee explained how money was spent from 1996 to 2001 in an article entitled: "The Promotion and Marketing of Oxycontin: Commercial Triumph, Public Health Tragedy" (9). "Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona, and California," he wrote. "More than 5000 physicians, pharmacists, and nurses attended these all-expenses-paid symposia, where they were recruited and trained for Purdue's national speaker bureau."

Another pillar to the marketing plan was the use of data. Purdue used a database of prescriber habits to identify the highest and lowest prescribers of particular drugs in a single zip code, county, state, or the entire country. The company then targeted the physicians who were the highest prescribers for opioids across the country.

As Chris McGreal details in his book, "American Overdose: The Opioid Tragedy in Three Acts," Purdue sales reps distributed coupons for doctors to give their patients a 30-day free supply of Oxycontin and would arrive at physicians' offices "loaded with free mugs, fishing hats, even a CD: Get in the Swing With Oxycontin." Sales of Oxycontin grew during this time from $48 million in 1996 to almost $1.1 billion in 2000.

But in 2001, the New York Times reported that a rapidly increasing number of people were bypassing the slow release formulation by crushing the pills and either inhaling the drug, or mixing it with liquid and injecting for a quick and powerful high (10). As our sidebar (The Opioid Crisis in Numbers) shows, 21 to 29 percent of patients prescribed opioids for chronic pain misuse them, with between 8 and 12

"Purdue sales reps had fraudulently downplayed the drug's potential for abuse – sometimes using fake scientific charts, which they distributed to doctors."

percent going on to develop an opioid use disorder. By 2004, Oxycontin had become a leading drug of abuse in the US (9).

Purdue was aware of the potential for addiction early: over a hundred internal company memos between 1997 and 1999 included the words "street value," "crush," or "snort" (10). But it wasn't until 2004 that the company was first sued – by the West Virginia Attorney General for reimbursement of "excessive prescription costs" paid by the state. The state charged Purdue with deceptive marketing, but the case never went to trial and Purdue agreed to settle with $10 million.

The most significant case came in 2007, when the company pleaded guilty to misleading the public about Oxycontin's risk of addiction and agreed to pay a $634.5 million settlement. Purdue sales reps had fraudulently downplayed the drug's potential for abuse – sometimes using fake scientific charts, which they distributed to doctors. Several senior executives of the company paid a total of $34.5 million in fines after pleading guilty to "misbranding" (11).

In May 2018, six states – Florida, Nevada, North Carolina, North Dakota, Tennessee and Texas – filed lawsuits charging deceptive marketing practices, adding to 16 previously filed lawsuits by other US states and Puerto Rico. By September 2019, over 2000 plaintiffs – including 23 states, local governments and Native American tribes were suing Purdue.

At the time of writing, Purdue had reportedly reached a tentative $10-12 billion deal, in which the Sackler family would exit the company before it filed for bankruptcy, dissolved and reformed. But the company could still face legal battles with states not in the deal, such as Connecticut, Iowa, Massachusetts, Nevada, New Jersey, New York, Pennsylvania, North Carolina and Wisconsin (12).

MARKETING OPIOID THERAPIES

Another opioid that has made headlines in the US is fentanyl, a fast-acting, high-potency drug that is 50 times more powerful than morphine. Originally, fentanyl was rarely used outside of hospital operating rooms, but following the introduction of a transdermal formulation of the drug in the 1990s, it became an option for chronic pain management. As its popularity increased, alternative forms of the drug, including lozenges, tablets, and sprays were developed for medical use (13).

As these formulations can be more easily mixed with other drugs to increase bulk or potency, fentanyl grew in popularity among drug dealers as a cutting agent for a variety of drugs. From 2010 to 2016, there was a three-fold increase in the

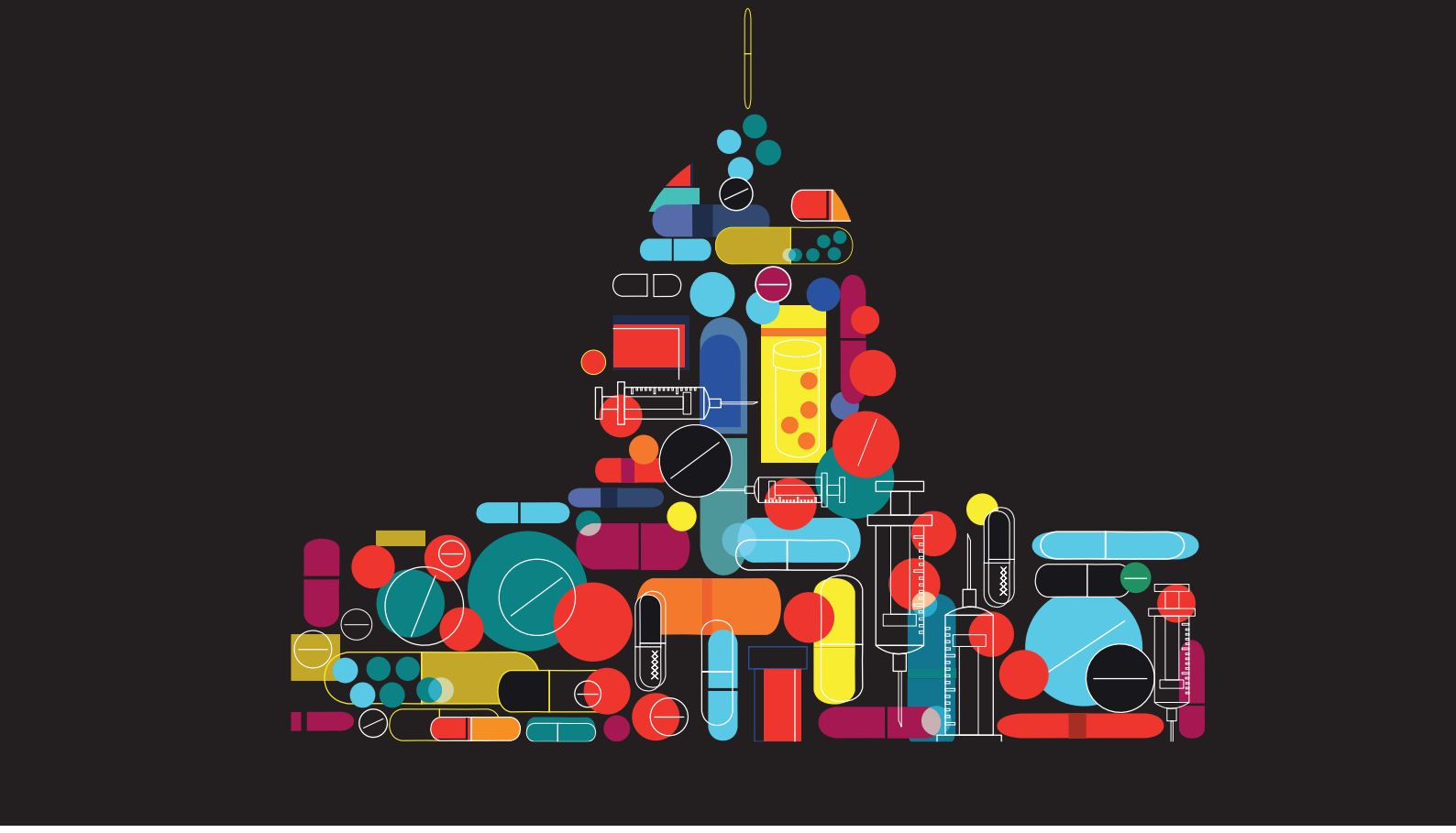
A FEW BAD APPLES?

A central question faces pharma in the wake of the ongoing opioid crisis: can the industry's contribution be attributed to only a few bad apples or is it a signal of a wider problem?

Thuy Nguyen, Postdoctoral Fellow at the O'Neill School of Public and Environmental Affairs, Indiana University Bloomington, US, set out to understand the link between payments to physicians and opioids prescribing on a nationwide scale.

"Well-documented cases and lawsuits of marketing of Oxycontin and Subsys indicate that many opioid-related marketing practices are problematic and tremendously harmful to public health," says Nguyen. "Our recent paper provides evidence of the problematic role of opioid-related promotion in the US opioid crisis."

The researchers found that the US doctors who received pharmaceutical payments from 2014 to 2016 prescribed, on average, over 13,070 daily doses of opioids per year more than their colleagues that received no such payments (17). "Although this finding should not be interpreted as causality, this substantial association, together with well-documented cases and lawsuits of marketing of Oxycontin and Subsys, provide support for the necessity of enhanced transparency and efficient restrictions regarding pharmaceutical marketing," Nguyen says.



proportion of opioid deaths caused by synthetic opioids like fentanyl. By December 2018, fentanyl was the most commonly used drug in overdose cases (14).

One such spray was a sublingual formulation called Subsys, developed by Insys Therapeutics. The FDA approved the drug for "breakthrough pain" in cancer patients that persist after using other medications. Following the approval in 2012, Insys became the US's best performing IPO, and by 2015, revenue from Subsys approached $500 million (15).

But as MotherJones reports, several Insys employees were simultaneously filing whistleblower lawsuits alleging that the addictive drug was marketed, off-label, to patients who suffered from all kinds of pain, and detailing dubious sales tactics – including, allegedly, taking doctors to strip clubs, encouraging sales reps to sleep with and give lap-dances to doctors, hiring doctors' significant others, paying kickbacks for more prescriptions, compensating physicians for speaking at events based on the volume of Subsys prescriptions written, and posing as doctors' representatives to get insurance to cover the drug (15).

On May, 2019, a federal jury found top executives of Insys Therapeutics, including the one-time billionaire John Kapoor, guilty of racketeering charges. They were found to have conspired to fuel sales of Subsys by bribing doctors and misleading insurers about patients' need for the drug. The company agreed to pay $225 million to settle the federal government's criminal and civil investigations into the company's marketing practices. The company filed for bankruptcy 10 days later (16).

WIDESPREAD LITIGATION

Purdue and Insys are by no means the only companies facing lawsuits related to the opioid crisis. The State of Ohio has taken a number of opioid manufacturers to court, including Teva, J&J, Janssen, Endo, Allergan and Actavis. They allege the companies disseminated deceptive statements about opioids and misrepresented the risks and benefits through marketing schemes.

In the lawsuit, the authors write, "Each Defendant used both direct marketing and unbranded advertising disseminated by seemingly independent third parties to spread false and deceptive statements about the risks and benefits of long-term opioid use." They cite the example of one of Endo's ads that included photographs depicting patients with physically demanding jobs like construction workers and chefs, which they say misleadingly implied that the drug would provide long-term pain-relief and functional improvement (18). They also cite a patient education guide, distributed by Janssen, which claimed that "[m]any studies show that opioids are rarely addictive when used properly for the management of chronic pain."

AN INTERNATIONAL ISSUE

Eighty percent of the world's prescription opioids are consumed in the USA, but it isn't the only country with opioid misuse problems. That said, the USA's death rate is double that of the Nordic and Anglophone countries, which have the next highest rates, and more than 27 times higher than in Italy and Japan. On average, drug overdose death rates in the USA are 3.5 times higher when compared to 17 other high-income countries (24).

According to the authors of the study, this phenomenon is fairly recent – "in the late 1990s and early 2000s, the Nordic countries had the highest levels of drug overdose mortality," they said.

The researchers found that, in terms of its trends in and age profile of drug overdose mortality, Canada is the country that most closely resembles the USA, with prescription opioids playing a "key role" in driving drug overdose mortality in both countries.

Canada is the second highest per capita user of prescription opioids in the world. Fatal overdoses in Ontario, Canada's largest province by population, are almost as common as in the USA and roughly twice as common as in England and Wales (25). Canada also has problems with street fentanyl, often produced overseas. According to David Juurlink, Head of Clinical Pharmacology and Toxicology at Sunnybrook Health Sciences Centre in Toronto (quoted in the BMJ), the street fentanyl problem is "a response to the demand created by doctors prescribing opioids so wantonly for the past 20 years."

The authors list several factors contributing to high USA drug overdose mortality:

Health care system factors:

- Other countries typically placed greater restrictions on strong opioids like oxycodone for non-cancer pain treatment
- Regulations regarding opioid use in European countries included: dose limits, requirements that patients be registered to receive opioid prescriptions, use of duplicate or triplicate prescription pads, and use of special prescription forms
- Reimbursement policies in the USA promote greater reliance on opioid prescribing because insurers in the USA are more likely to cover prescription drugs for chronic pain than alternative therapies, which may be classified as "experimental"
- Prescription opioids are the lowest-cost option for many patients in the USA
- The USA appears to be an outlier in terms of the use of psychotropic drugs, including benzodiazepines, which act synergistically with prescription opioids to increase mortality
- Fee-for-service is the dominant payment method in the US, whereas the set of countries with the lowest drug overdose mortality (Austria, Italy, Japan, Spain, and Portugal) have a much greater reliance on capitation or salary systems
- It is more difficult for physicians to identify doctor shopping due to the poor quality, lack, or underutilization of centralized administrative patient records, and prescription drug monitoring programs remain underused and vary in terms of quality and completeness across states

Pharmaceutical industry factors:

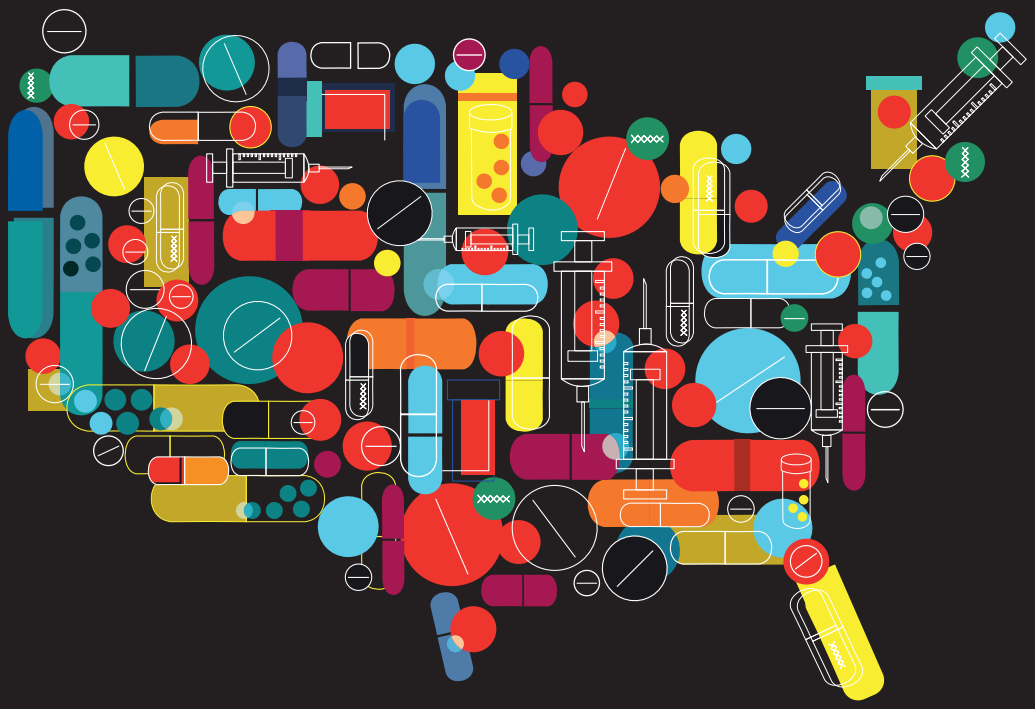
- Opioid prescribing can also be motivated by pharmaceutical advertising and marketing; and only the US, New Zealand and Brazil permit direct-to-consumer advertising
- The majority of new drugs are approved in the USA before other countries and all five countries with the lowest drug overdose mortality approved Oxycontin fairly late and have relatively low approved maximum dosage forms

Drug policy factors:

- The USA favors abstinence-only policies, which (according to the authors) have been hypothesized to contribute to riskier drug use, less access to treatment, and higher drug overdose mortality
- Compared with other countries, the USA has a much lower percentage of opioid-dependent patients in treatment
- Buprenorphine is expensive and difficult to access in the US. France's policy to allow all registered medical doctors to prescribe buprenorphine without any special education or licensing was associated with a tenfold increase in patients being treated and a 79 percent reduction in opiate deaths

Other factors:

- In an environment where patients have wide choice and can easily change providers, physicians have stronger incentives to placate patients by prescribing painkillers
- The USA has a higher prevalence of pain-related chronic diseases and disability
- Poor macroeconomic conditions contributing to unemployment, deindustrialization, and downward intergenerational mobility



Former Ohio Attorney General, Mike DeWine, claimed opioid companies spent "millions of dollars on promotional activities and materials that falsely deny or trivialize the risks of opioids while overstating the benefits of using them for chronic pain." He argued that opioid makers were "borrowing a page from Big Tobacco's playbook" (19).

In a case in Oklahoma, a judge ruled that J&J had intentionally played down the dangers and oversold the benefits of opioids. The company was ordered to pay the state $572 million. There are currently more than 2,000 opioid lawsuits pending across the US pursuing a legal strategy similar to Oklahoma's.

"In some ways, the J&J opioid lawsuit decision by Judge Balkman is a 'litmus test' for future opioid cases," says Rebecca Haffajee, Policy Researcher at RAND Corporation and Adjunct Assistant Professor of Health Management and Policy at the University of Michigan. "The misleading and deceptive marketing behavior that the Judge found J&J guilty of, in violation of the state's public nuisance law, is behavior this company and many others appear to have engaged in, in other states and locales, where they are defending similar lawsuits."

The Oklahoma case was interesting in that it potentially sets a precedent for holding a manufacturer legally responsible for creating a public nuisance by selling opioid products. "In the past, this legal theory has been successfully asserted in cases of real property destruction," says Haffajee. "The outcome of this case may induce opioid manufacturers and distributors to favor settling, rather than going to trial, in other cases to avoid potentially arge payouts and negative publicity."

But Haffajee thinks there are a few reasons to think the Oklahoma case will not "set the rule" for other cases. "Johnson and Johnson plans to appeal the ruling, so it could potentially be overturned; as well, the public nuisance law in Oklahoma is more broad and favorable to the government than are sister laws in other states," she says. "Other legal theories (such as fraud and unjust enrichment) are more prominent in many other cases."

Another legal argument being pursued in many states is that opioid distributors did not do enough to stop controlled substances from being misused. A lawsuit in the Cherokee Nation against McKesson, Cardinal Health, Amerisourcebergen,

CVS, Walgreens Boots Alliance and Wal-Mart alleges that the defendants "utterly failed" in their duty to "serve as a check in the drug delivery system, i.e., by securing and monitoring opioids at every step as they travel through commerce, protecting them from theft, and refusing to fill suspicious or unusual orders by downstream pharmacies, doctors, or patients," (20).

McKesson, CVS, Walgreens and Cardinal Health have already paid fines and settlements for the opioid crisis, sometimes multiple times over (21).

THE RESPONSE

Although the number of drug overdose deaths fell for the first time since the crisis began in 2018, a report by RAND in August 2018 found that the rise of fentanyl and its analogs largely in the Northeast and Midwestern areas of the US could spread (22). The report concludes that problems with synthetic opioids are likely to get worse before they get better. "The US synthetic opioid problem is not yet truly national in scope," said the authors. "Some regions west of the Mississippi have been less affected to date. Those areas should be seen as at high risk of a worsening problem." Sadly, reports from San Francisco and Seattle suggest the report's grim predictions may be coming true (23).

What could be done in the short term to alleviate the number of Americans dying from opioid overdoses? According to Tom Frieden, access to opioid agonist therapy is key. "We need a complete change in the way we enable access to buprenorphine such that it is no harder – and ideally slightly easier – to prescribe than other opiates," he says. Buprenorphine effectively binds to the same brain receptors as opioids used for pain and is used to lower the potential for misuse, diminish the effects of physical dependency to opioids and increase safety in cases of overdose. "This, combined with barrier-free access to treatment with buprenorphine and methadone, and widespread availability of naloxone, would be the most likely means to rapidly reduce deaths from opiates."

Longer term, many have called for regulatory responses to the opioid crisis and have argued that the FDA should have done more, or acted differently, during the crisis. For example, the FDA has been criticized for approving Oxycontin's original label, as mentioned previously. The FDA has also faced criticism for facilitating "regulatory gamesmanship" (26) by approving Purdue's reformulation of Oxycontin (Oxycontin OP) while at the same time removing the original formulation from the market on safety grounds, thus preventing generic competition and ensuring the continuation of Purdue's monopoly.

Some have also questioned the FDA's closeness to the industry. For example, two medical officers, who originally approved Oxycontin, Curtis Wright and Douglas Kramer, went to Purdue Pharma shortly after leaving the FDA.

"Commentators often blame FDA reluctance on capture by the drug industry (and there is certainly some truth to that), but I argued in my paper (27) and elsewhere that the agency is excessively deferential to the medical community and avoids stepping on the proverbial toes of physicians," says Lars Noah, Professor of Law at the University of Florida, who has been writing about the opioid crisis since 2002. "I continue to focus on primary prevention (ban off-label use and mandate physician certification rather than letting any clown with prescribing privileges and a DEA number hand these out like candy) while recognizing that opiate-use disorder (OUD) treatment is the critical need," he says.

Tom Frieden also points towards FDA reform. "Congress needs to change the law so the FDA is not forced to approve all medicines which are shown to be equivalently safe and effective," he says. "The law should also allow the FDA to restrict promotion, advertising, and so-called medical education that actually serves to market products to doctors in ways that are not in the public interest."

Since 2013, USA manufacturers have had to report their financial ties with prescribers, as mandated by the Physician Payment Sunshine Act. "But a recent paper by King and Bearman (28) suggests that banning or limiting pharmaceutical gifts to doctors are more effective in reducing the influence of marketing on prescribing decisions than disclosure policies alone," says Thuy Nguyen, Postdoctoral Fellow at the O'Neill School of Public and Environmental Affairs, Indiana University Bloomington. "Vermont, Massachusetts and Minnesota already implemented such statutory bans at the state level."

Nguyen also argues that training of prescribers by academics or public health workers, commonly known as academic detailing, can be considered as an alternative way to provide information of beneficial new drugs with advantages of minimal bias and profit-seeking. "For example, medications to treat opioid use disorder (MOUDs) have been found to decrease mortality and morbidity associated with this type of disorder," she says. "Academics or public health workers without financial ties with manufacturers of these drugs could provide information of the risks and benefits."

Finally, Nguyen points out that training in the ethics involved in accepting pharma manufacturer financial incentives should also be considered, as prior research has shown that attending a medical school with a gift restriction policy reduces the prescribing of marketed products (28). "Continuing ethical education can enhance prescribers and medical staff's awareness of potential conflicts of interest and help them to effectively resolve or manage these conflicts," she says

THE BIG PICTURE

It is important not to forget about the millions of Americans who suffer with chronic pain and take opioids for much-needed relief. There is an important distinction to be made between being "dependent on" and misusing a drug: there are many patients that legitimately need and take opioids – sometimes increasingly stronger drugs over time. As mentioned previously, they are the clear majority of patients taking opioids. Any efforts to curb opioid approvals or prescriptions should be wary of leaving such patients without help.

Indeed, new CDC guidelines in 2016 advised clinicians to prescribe the lowest effective dose of an opioid and to monitor carefully for benefit and risks when considering dose increase. But, as Beth Darnall argues in Pain Medicine, some healthcare organizations and states have misapplied these guidelines to mandated opioid tapering in patients taking long-term opioid prescriptions (29). Darnall states that this has led to "serious and grave patient harm" and notes "reports of depression, suffering, and patient suicides during forced opioid tapering have increased at alarming rates, and advocacy groups have begun curating patient suicide registries."

Those arguing for the expansion of opioid treatments did not always adequately report the potential for misuse. And the opioid crisis raises painful questions about the actions of pharma companies and conflicts of interest within regulatory bodies and the healthcare profession. But it must not be forgotten that the original expansion was in response to a real public health problem: chronic cancer pain.

Eighty percent of patients with advanced cancer experience moderate to severe cancer pain, and approximately 55 percent of patients with cancer and 40 percent of survivors experience chronic cancer-related pain. Yet a recent meta analysis of 122 studies found that one-third or more patients with cancer and survivors are having difficulty getting access to their prescribed opioid medications and that the proportion of people experiencing such difficulties has increased markedly since 2016 (30).

But Frieden goes so far as to say chronic pain should rarely if ever be newly treated with opioids. "Opioid naive patients (patients who have never been on an opioid) should be treated with physical therapy, local measures, Tylenol, Motrin or other NSAIDs, and cognitive-behavioral therapy instead – these alternatives all work and are much safer than opioids. They preserve function better, and, unlike opioids, don't potentiate and increase pain perception," he says. "For people on opioids, measures to reduce the risk of fatal overdose are key. And for those who are addicted, increasing access to effective treatment can save lives."

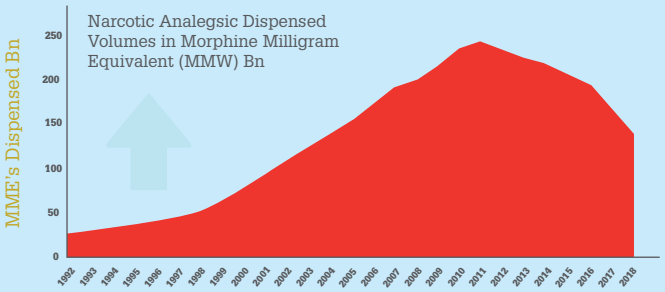
In the coming years, the healthcare profession will have to reconcile the need for effective treatments for individuals suffering with chronic pain and the tremendous costs of the opioid crisis – especially in terms of human life, the impact on families and communities, as well as society at large.

More information, including a full list of references, can be found in the online version of this article, available at www.themedicinemaker.com.

THE OPIOID CRISIS IN NUMBERS

PRESCRIBING

Opioid prescriptions **peaked** in **2011**



21 to 29%

of patients **prescribed opioids** for chronic pain **misuse** them

BETWEEN 8% AND 12%

develop an opioid use disorder

An estimated 4-6%

who **misuse** prescription opioids transition to **heroin**

80%

of people who use **heroin** first misused **prescription opioids**

COSTS

$504 *billion*

is one estimate of the total cost of the opioid crisis to USA society

2.5%

of **US** GDP in **2015**

Total "ECONOMIC BURDEN" of prescription opioid misuse alone in the USA is *$78.5 billion* a year

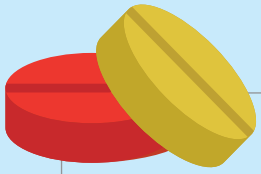
- Healthcare
- Lost productivity
- Addiction treatment
- Criminal justice involvement

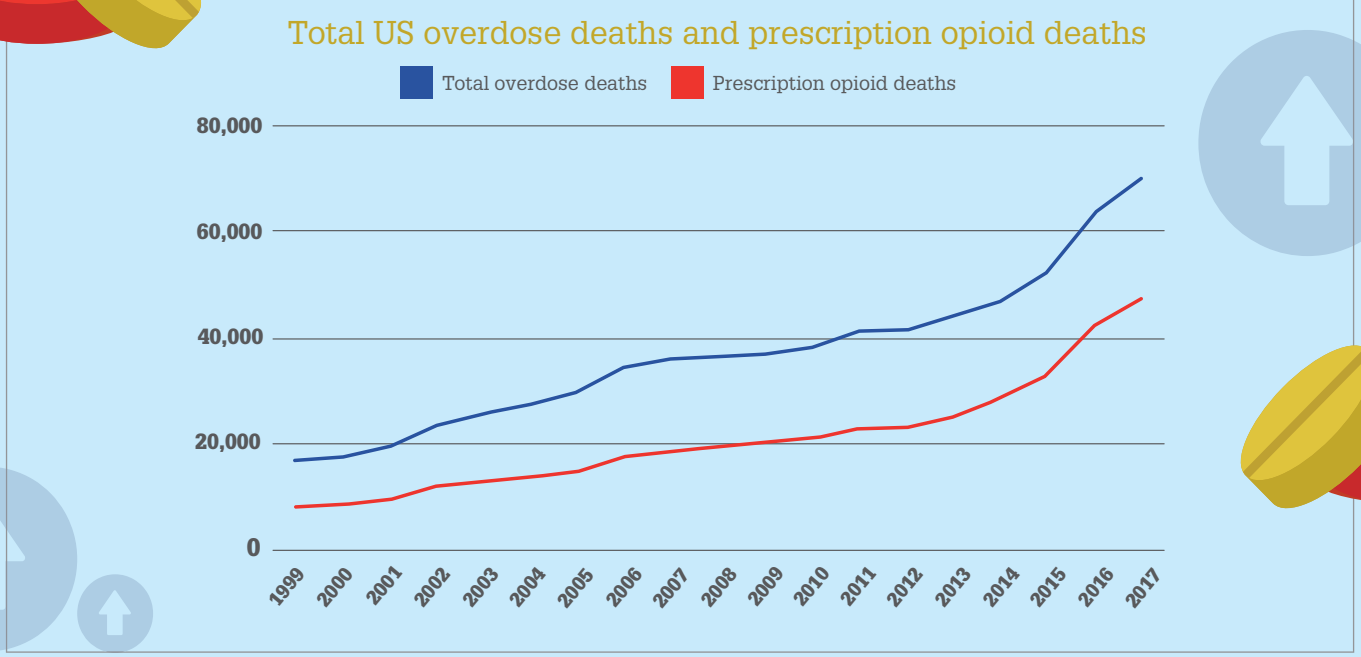
Total Medicaid costs associated with opioid use disorder more than tripled between **1999** and **2013** to **$3 billion**

the Medicine Maker

Sources: IQVIA, "Medicine use and spending in the U.S." (2019). Available at: https://bit.ly/2HcsZgQ. Last accessed September 5, 2019. NIH, "Opioid overdose crisis" (2019). Available at: https://bit.ly/2j6YEE1. Last accessed September 5, 2019. CDC, "Opioid overdose" (2019). Available at: https://bit.ly/2b8LbS3. Last accessed September 5, 2019.SA Ryan, "Calculating the real costs of the opioid crisis" (2019). Available at: https://bit.ly/2lFXJOT. Last accessed September 5, 2019.Penn State, "Researchers estimate societal costs of the opioid epidemic" (2019). Available at: https://bit.ly/2lFN72s. Last accessed September 5, 2019.

OVERDOSES





PENNSYLVANIA: A SNAPSHOT

Opioid misuse reduced Pennsylvania state tax revenue by over

$11 billion

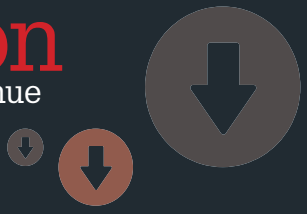
Approximately

$10 billion

in lost income tax revenue and more than

$1 billion

in lost sales tax revenue



Between **2007** and **2016,** total costs to Pennsylvania's criminal justice system from the opioid crisis was over

$526 million

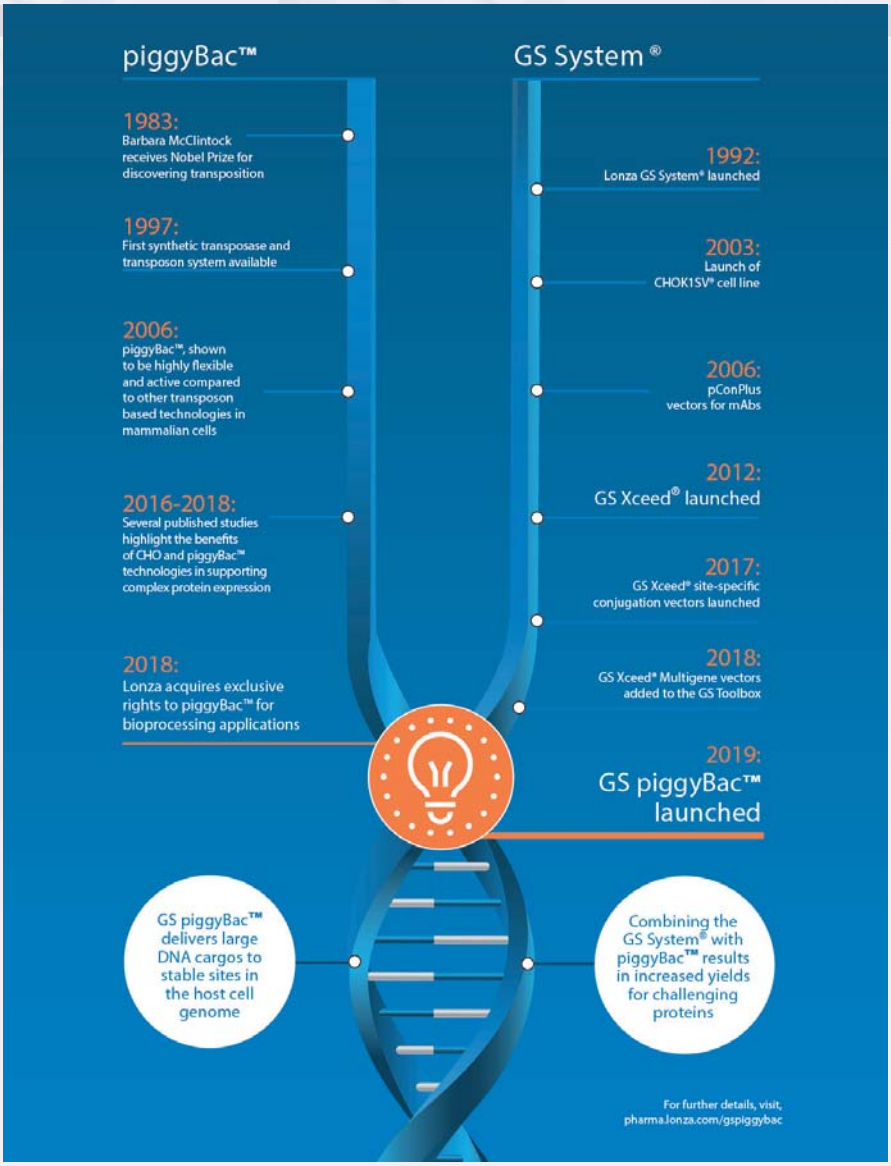
Total annual education costs for children born in Pennsylvania with neonatal abstinence syndrome associated with maternal use of prescription opioids: over

$1 million

When One Size Doesn't Fit All

More complex proteins are coming down the pipe, but bispecifics and other novel format antibodies or glycoproteins – with domains combined from various molecules and unnatural engineered elements – can't always be easily shoehorned into existing platforms. Instead, next-generation protein expression will require a toolbox of next-generation solutions.

By Alison Porter



Biological systems have been used to produce therapeutic proteins since 1982, when Humulin (human insulin) was approved by the FDA as the first recombinant biopharmaceutical. Since then, biopharma has grown tremendously; in particular, monoclonal antibodies (mAbs), which continue to be the largest and fastest growing biopharmaceuticals – doubling in market-size over the past five years (1). However, peer into biopharma pipelines and you will find an abundance of more complicated, difficult-to-express molecules – next generation biologics.

The term "complex molecules" can be controversial in scientific circles. Colleagues will be quick to point out that anything beyond a simple protein, including a traditional mAb, is technically "complex." I use the term colloquially to refer to molecules that go beyond standard antibodies. Examples would be bispecifics or other novel antibody formats or glycoproteins that combine domains from various molecules, often including engineered elements that you won't find in nature. These are, naturally, difficult to express in existing expression platforms.

Another example of a problem manufacturers face is that these molecules will sometimes require additional genes when compared to the two required for a vanilla antibody. Here, simply getting all of the genes into a cell may be difficult, and pairing of gene products once in the system, if required, can be a real challenge. Equally, challenges exist during downstream and upstream development: purification can be tricky, especially if the protein is lacking an Fc region.

Faced with these difficulties, many in the industry have tried to shoehorn complex proteins into existing platforms, but this often results in a great deal of time and effort spent trying to find a suitable cell line and process. Trying to use existing systems can also mean there is a danger that important points are missed. For example, it can be vital to consider product quality, as well as product concentration, early in the process. We know these molecules can be difficult to express, so finding the best expressing cell line is important. But if product concentration alone is the main focus, a suitably expressing cell line could be selected, but it may not achieve the desired target product profile.

A toolbox of solutions

With monoclonal antibodies, technologies have been developed that can deal with the same molecule type again and again. Increasingly, however, expression platforms must deal with molecules of different "sizes and configurations," so a one-size-fits-all approach doesn't work as well.

Developing a toolbox of solutions to deal with the variety of complex proteins coming down the pipe will be essential. For example,

at Lonza we have developed a multigene vector system that allows the transfection of multiple genes simultaneously on a single vector. This is far simpler and easier than two alternative approaches available today: namely co-transfection and what I would call a "mix-and-match" approach.

The mix-and-match approach involves constructing several cell lines where each makes a portion of the product. Fully purified material from each can then be mixed together and the product chemically recombined. This would be followed by a purification step to clean up and obtain the desired end product. Technically this can work, but the time and cost associated with making several cell lines can be significant.

Co-transfection, on the other hand, involves spreading your genes of interest out over multiple vectors and transfecting them all at the same time. This does avoid the need to make several cell lines, but there are several disadvantages. For example, you may need additional selection markers, which may be difficult to source. There can also be further analytical work required to identify the cell lines that have taken up the vectors and are expressing each of the genes at the required amount. Additionally, there is an increased risk of cell line instability when using multiple vectors as individual vectors can be lost. A multigene vector system, on the other hand, can be seen as the best of both worlds, since it removes the need to make several cell lines, without the additional work and risk associated with co-transfection.

Another important tool in the protein expression toolbox is Lonza's GS piggyBac™ transposon-based technology, which is also well suited to more complex proteins. Transposons are mobile genetic elements and their mobility is mediated by transposase enzymes. The transposon, as part of a DNA vector, contains the genes you want to insert into your host cell, surrounded by inverted terminal repeat sequences. Once the vector is introduced into the host cell along with the enzyme, the transposase recognizes the inverted terminal repeat sequences at each end of the genes you want to move, at which point the transposase cleaves the DNA. The target gene is then pasted into specific sites within the genome associated with stable, high expression. These sites have a specific sequence (TTAA) and are found within regions of open chromatin. The combination of GS System® and piggyBac™ technologies therefore allows you to select cell lines where vectors have been inserted into highly transcriptionally active sites that are associated with stable, high expression.

This system can deal with the large gene cargos that are often associated with complex proteins (it has a cargo capacity of over 200 kb). GS piggyBac™ can preferentially target genetically stable parts of the genome at high efficiencies, which means that, it also has the potential to improve cell line stability.

The key benefit of GS piggyBac™ is that it works very well for low-expressing proteins, which complex proteins often are. For example, in 2016, a group at Eli Lilly tried combining piggyBac™ with GS CHO technology with four different antibodies, including a bispecific antibody (2). A two- to twelve-fold increase in product concentration was observed with piggyBac™ compared to control CHO pools – and in follow on work (2017) this group demonstrated that product quality was similar between piggyBac™ and control pools. They concluded in this follow on work that the higher product concentration could be explained by a combination of increased average gene copy number, significantly higher messenger RNA levels and the homogeneity of the piggyBac™ pools, relative to the control (3).

Lonza has carried out proof-of-concept studies with GS piggyBac™. Using a difficult-to-express antibody – one expressing less than one gram per liter (pretty poor for an antibody), we observed a >200 percent increase in product concentration with GS piggyBac™ compared to the control. Lonza's commitment to ongoing technology advancements of our expression systems has resulted in us evaluating a number of different technologies alongside GS. Increases in product concentration of the scale observed with these studies are rare.

The ripple effect

The benefits of improving expression levels are clear when one thinks about cost and efficiency upstream, but they also have further benefits. For example, if you have low expression levels with a complex protein then you might have to extend your cell line construction to try and find a good expresser, or you may have to perform multiple rounds of process optimization to improve product concentration. This can be time consuming and can extend development timelines. This is a problem for the industry as a whole, but especially for small biotechs who are under intense pressure to get ahead of the pack.

It's far too early to write off mAbs – they will continue to play a prominent role in biologic medicine for the foreseeable future. But as developers look to move beyond the low-hanging fruit by tinkering with nature to create new, responsive drug systems, complexity and variety will eventually become the norm. But these new therapies will never fulfill their therapeutic potential unless manufacturers are able to achieve appropriate expression levels whilst meeting the desired target product profile. And for that, a toolbox of solutions, tailored to each molecule will be key.

Alison Porter is Head of Expression System Sciences at Lonza.

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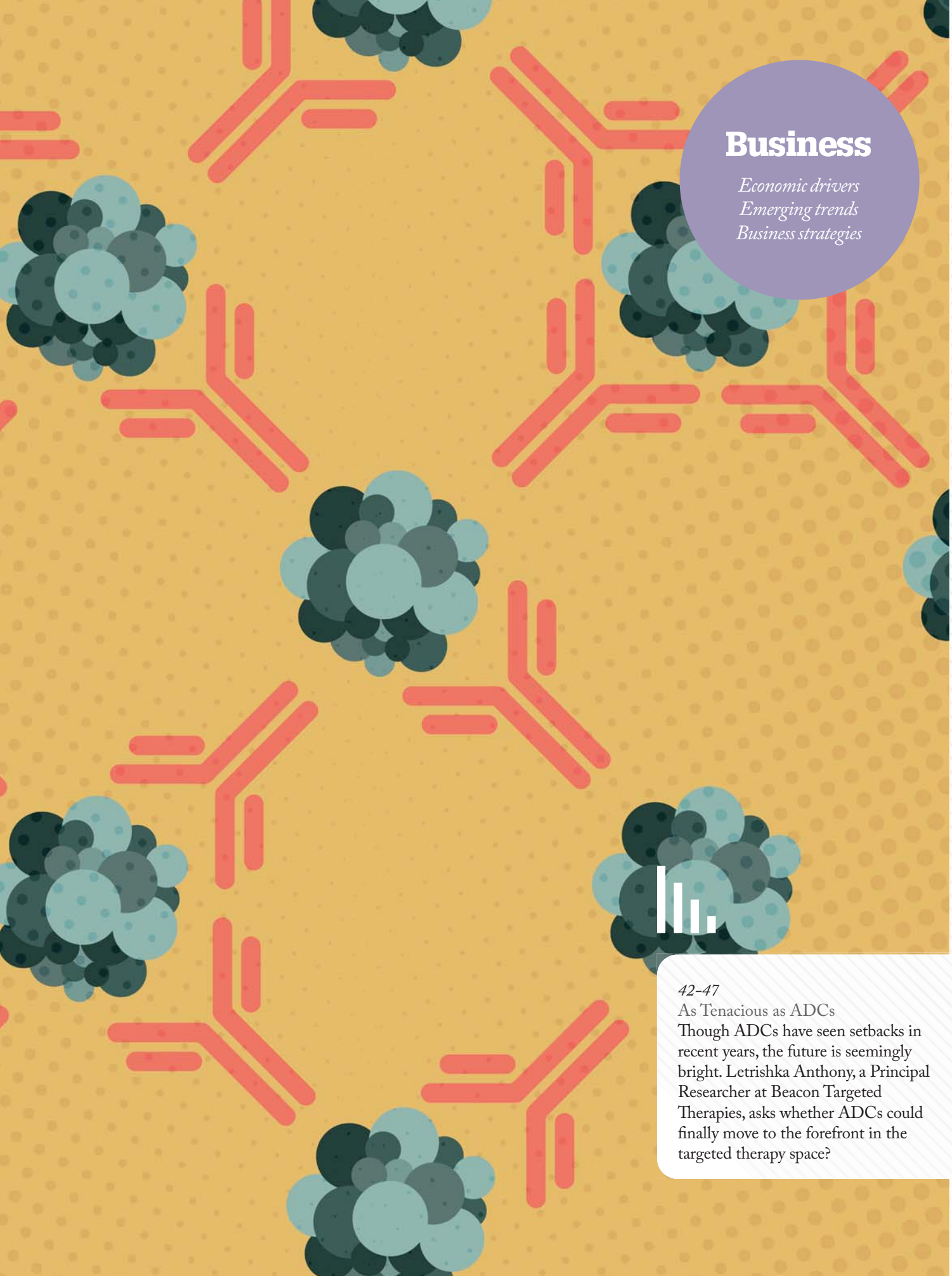
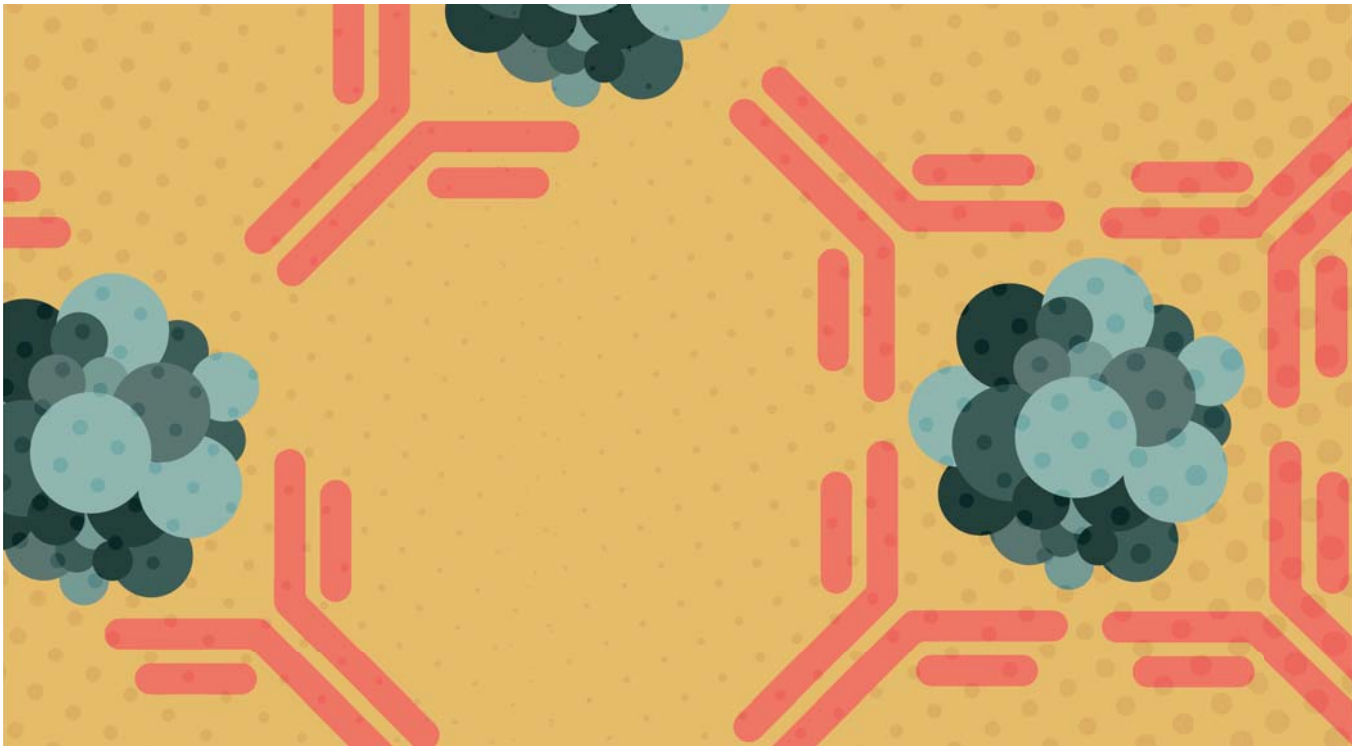


Business

Economic drivers
Emerging trends
Business strategies



As Tenacious as ADCs

After disappointment comes success: after a new approval and multi-million dollar deals, are ADCs finally on the verge of rising to the forefront of targeted therapies?

By Letrishka Anthony

In March 2019, a global development and agreement worth up to $6.9 billion was made between global pharmaceutical giants Daichii-Sankyo and AstraZeneca for DS-8201. This is quite remarkable because DS-8201 is, in fact, an antibody drug conjugate (ADC) – and it's fair to say that ADCs have faced a bit of adversity over the years. Plagued by higher than average discontinuation rates in recent years, the ADC space has also been hit by some high-profile setbacks, including AbbVie's frustration with disappointing results from one of its flagship investments, Stemcentrx's rovalpituzumab tesirine (Rova-T).

But now, after more than 20 years of development, ADCs are becoming a highly investible class of drugs. Why? The field recently witnessed its fifth approval (see Table 1) and boasts over 700 trials, more than 300 clinical and preclinical programs, annual growth in clinical trial starts and a growing number of new molecular entities entering clinic, according to Beacon Targeted Therapies.

In its most basic form, ADCs are comprised of a targeting moiety and payload. They essentially embody the Nobel Prize winning physician, Paul Ehrlich's "magic bullet" concept, articulated more than 100 years ago.

"Plagued by higher than average discontinuation rates in recent years, the ADC space has also been hit by some high-profile setbacks."

The payload is a cytotoxic compound, hitched to the antibody that – in an ideal world – drives selective binding directly to the desired site of action on a cancer cell.

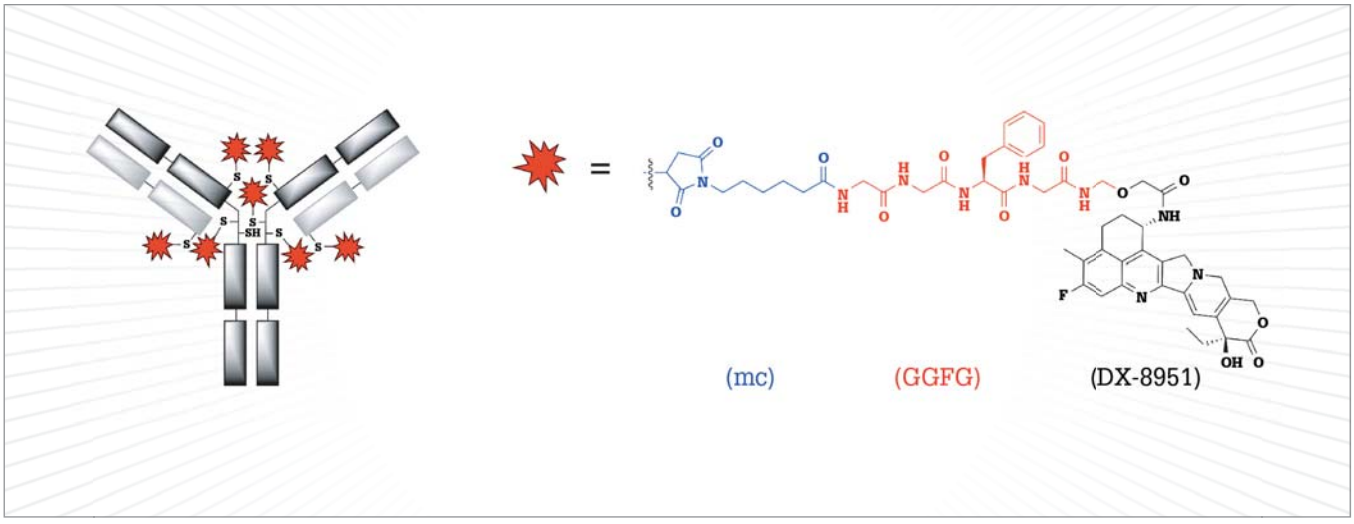
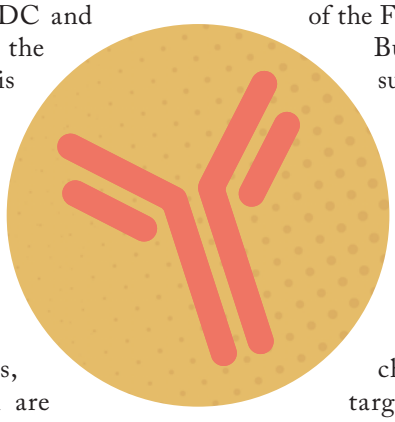


Figure 1. Structure of the antibody drug conjugate DS-8201; mc-GGFG = peptide linker; DX-8951 = payload.

However, the devil is in the details... Besides the targeting moiety and payload, there is a middle part that brings it all together, the linker. The specific linker and the mode of attachment (conjugation technology) employed contribute fundamentally to the properties of an ADC and so play a crucial role in the success or failure of this complex molecule.

Building a successful ADC

What do you need to know about optimizing antibodies to build an ADC? Over 100 different antibodies, the majority of which are humanized IgG1 monoclonal antibodies (mAbs), have been used to build ADCs. And more recently, some newer technologies have been implemented in order to enhance the performance of the antibody. Companies such as CytomX and BioAtla use conditionally active programmes where the antibody is activated to bind to the target only once in the tumour microenvironment, thus avoiding unwanted on-target binding in normal tissue. In a few cases, some companies such as GlaxoSmithKline and BioThera Solutions are even manipulating the antibody by enhancing the immunological activity of the Fc domain.



But after the clinical success of Genentech's Kadcyla, the human epidermal growth factor receptor 2 (HER2) targeting mAb, trastuzumab, has become a highly popular antibody choice. Indeed, as a target, HER2, is the target antigen of choice! It completely dominates the space, with a weighty 20 percent of clinically active ADCs targeting HER2 (18 of 90). The next most prevalent targets include TROP-2, Axl and c-Met at only 3 percent each.

What's even more striking with respect to HER2 is the global distribution of companies this target attracts. Daichii Sankyo's DS-8201 leads the way, currently engaged in 14 separate clinical trials, three of them being pivotal phase 3 studies, and a widely anticipated FDA submission is in sight for the end of the year. However, 50 percent of all HER2 targeting ADCs are currently being developed in China. In fact, the majority of ADCs to have entered the clinic in 2019 originate from Chinese developers, clearly, demonstrating the global interest in this space.

With regards to payloads, the tubulin inhibiting cytotoxins, auristatins and maytansines continue to dominate – comprising 47 percent of all clinical payloads – with industry powerhouses, Seattle Genetics and ImmunoGen out-licencing their linker-payload technologies to over 30 ADC developers. Their reputation is backed up by the approvals of Adcetris and Polivy and Kadcyla.

A range of payload potencies are

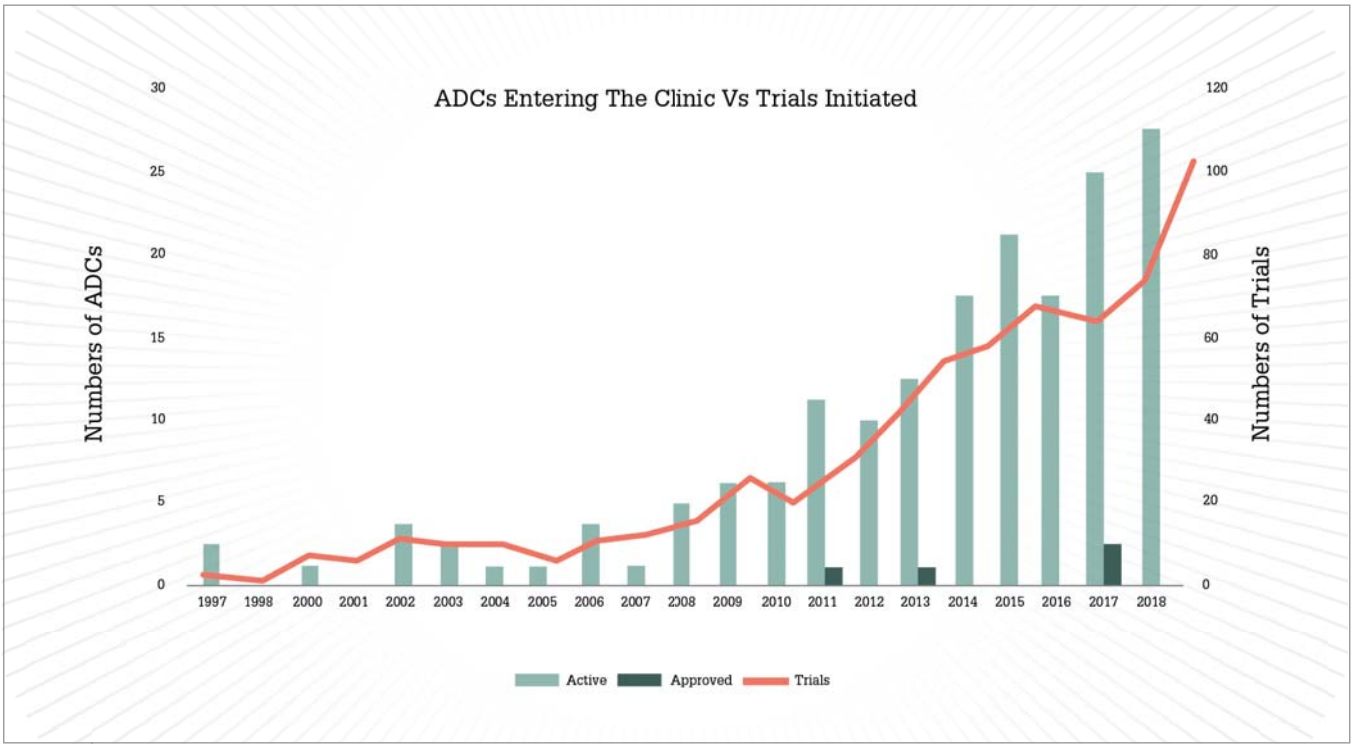
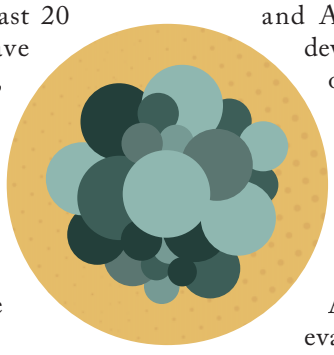


Figure 2. ADCs entering the clinic vs trials initiated. The orange line indicates the number of new clinical trials initiated per year for all ADCs undergoing clinical evaluation, with predicted growth. Light and dark green bars bars show the total number of ADCs entering into clinical evaluation in each year, and the number of ADCs approved in each year, respectively.

"The story of ADCs has proven to be one of tenacity and of pushing drug development boundaries through irrefutable innovation."

currently in use which, in turn, can dictate the drug to antibody ratio (DAR) of the ADC. The widely used auristatins and maytansines usually have an average DAR of about four. In contrast to this, the highly potent DNA cross-linking pyrrolobenzodiazepines (PBDs), of which at least 20 PBD-based ADCs have progressed into the clinic, typically have a lower DAR of about two. In some cases, using a less potent payload, DARs as high as 15 can be achieved, which is demonstrated by the work from Mersana.



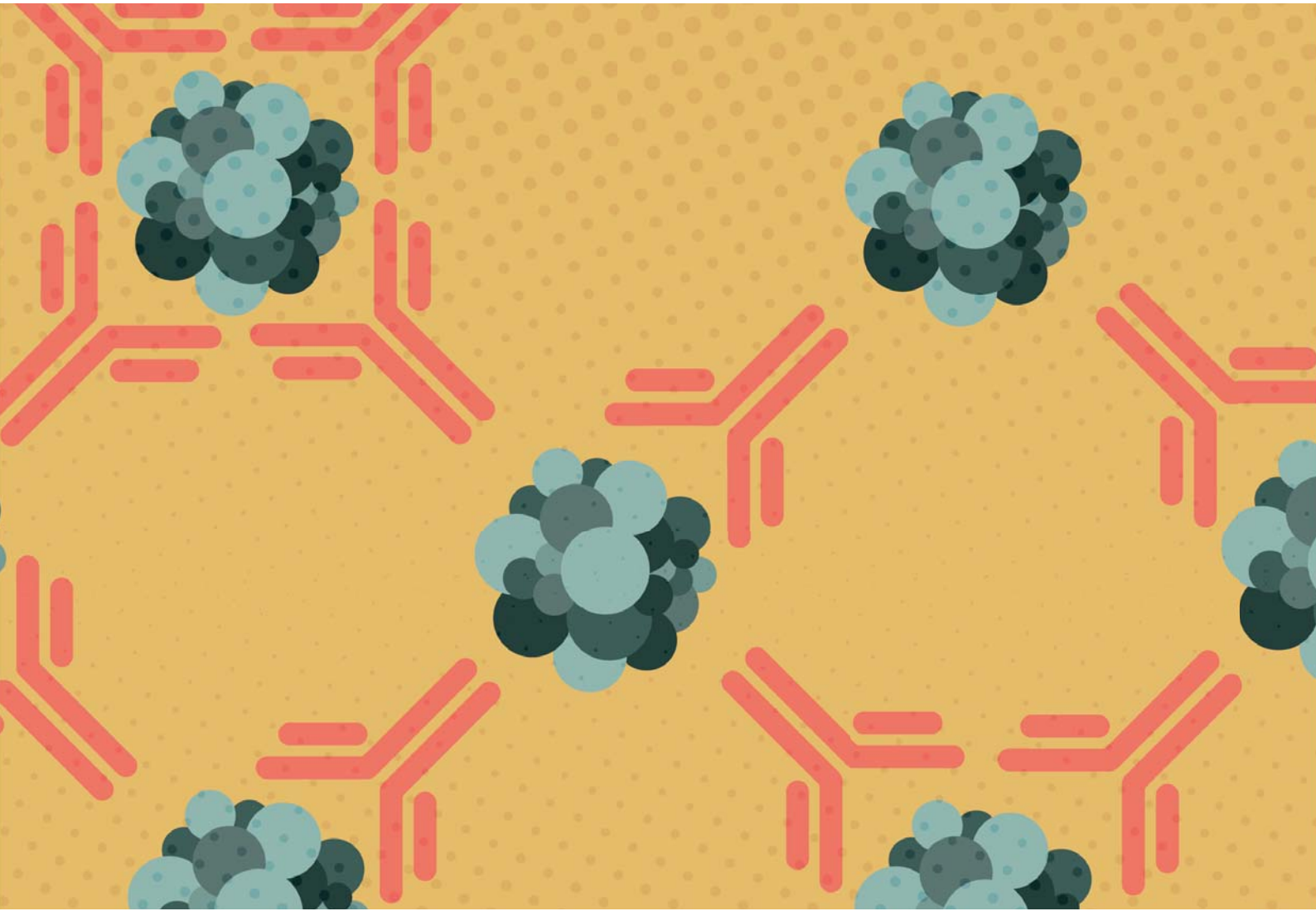
There is also an increasing number of novel payloads being developed, with varying mechanisms of action (MOAs), including DNA monoalkylators, topoisomerase I inhibitors, RNA polymerase inhibitors and, more recently, immunomodulators. Using alternative payloads and pushing the application of ADCs even further, companies such as Genentech and AbbVie have expanded development to indications outside of oncology. RG7861 incorporates an antibiotic agent for the treatment of methicillin-resistant Staphylococcus aureus and the steroid-based ABBV-3373 is undergoing evaluation in rheumatoid arthritis patients.

Link it all

Linkers, defined as the chemistry used to attach the payload to the antibody, play a crucial role in the delivery of the

ADC/ Developer	FDA Approval /Indication	Accelerated/Full Approval/2018 Sales	Target	Payload
Brentuximab vedotin (Adcetris) Seattle Genetics	• **August 2011**: Approval for R/R Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL) • **November 2017:** Approval for primary cutaneous ALCL and CD30 Mycosis Fungoides • **March 2018**: Approved as first line treatment with chemotherapy for stage III/IV Hodgkin's lymphoma • **November 2018**: Approved in combination with chemotherapy for adults with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas	• **2011**: Accelerated approval • **2015**: Full approval • **2018 Sales**: $476.9 million	CD30	MMAE
Ado-Trastuzumab emtansine (Kadcyla) Genentech	• **February 2013**: Approved for late stage breast cancer • **June 2017**: Kadcyla becomes available for routine use on NHS England • **May 2019**: Approved for adjuvant treatment of people with HER2+ early breast cancer with residual invasive disease after neoadjuvant treatment	• **2010**: FDA turns down accelerated approval request • **2013**: Full approval accepted by FDA • **2018 Sales**: $981 million	HER2	DM1
Inotuzumab ozogamicin (Besponsa) Pfizer	• **August 2017**: Approved for R/R acute lymphoblastic leukemia (ALL)	• **2017**: Full approval • **2018 Sales**: undisclosed	CD22	Calicheamicin
Gemtuzumab ozogamicin (Mylotarg) Pfizer	• **September 2017**: Approved for acute myeloid leukemia (AML)	• **2000**: Received accelerated approval • **2010**: Withdrawn • 2017: Full approval • **2018 Sales**: undisclosed	CD33	Calicheamicin
Polatuzumab vedotin (Polivy) Genentech	• **June 2019**: Approved for R/R diffuse large B cell lymphoma (DLBCL)	• **2019**: Accelerated approval • **2018 Sales**: N/A	CD79b	MMAE

Table 1: Approved ADCs, their approved indications, target and payload.



payload. A linker must avoid premature release of the cytotoxic payload and also ensure appropriate release of the payload as it binds to its target. There are two main linker families to choose from; the more widely used cleavable linkers, which cleave based on the physiological environment, and non-cleavable linkers, which rely on complete antibody degradation to release the payload upon internalization.

In terms of conjugation, a generational jump in approaches has been taken by drug developers to enhance the field. Whilst the clinic is still dominated by first generation techniques deploying stochastic conjugation to multiple natural lysines or cysteines on mAbs, there has been significant momentum in efforts directed toward more discrete, homogenous ADCs, utilising site-specific conjugation. Of the clinically active ADCs, over 20 percent are known to be site-specifically conjugated, and make up at least half of the ADCs that have entered the clinic in 2019.

The approaches range from genetic, such as the engineering of natural and non-natural amino acids at predefined antibody sites by companies such as Genentech, Seattle Genetics, Sutro Biopharma and Ambrx, to non-genetic routes explored through chemical and chemo-enzymatic techniques performed by the likes of Synaffix, Abzena, Catalent and Ajinomoto. However, this is still a relatively new development, with most site-specific ADCs still in phase I, it is

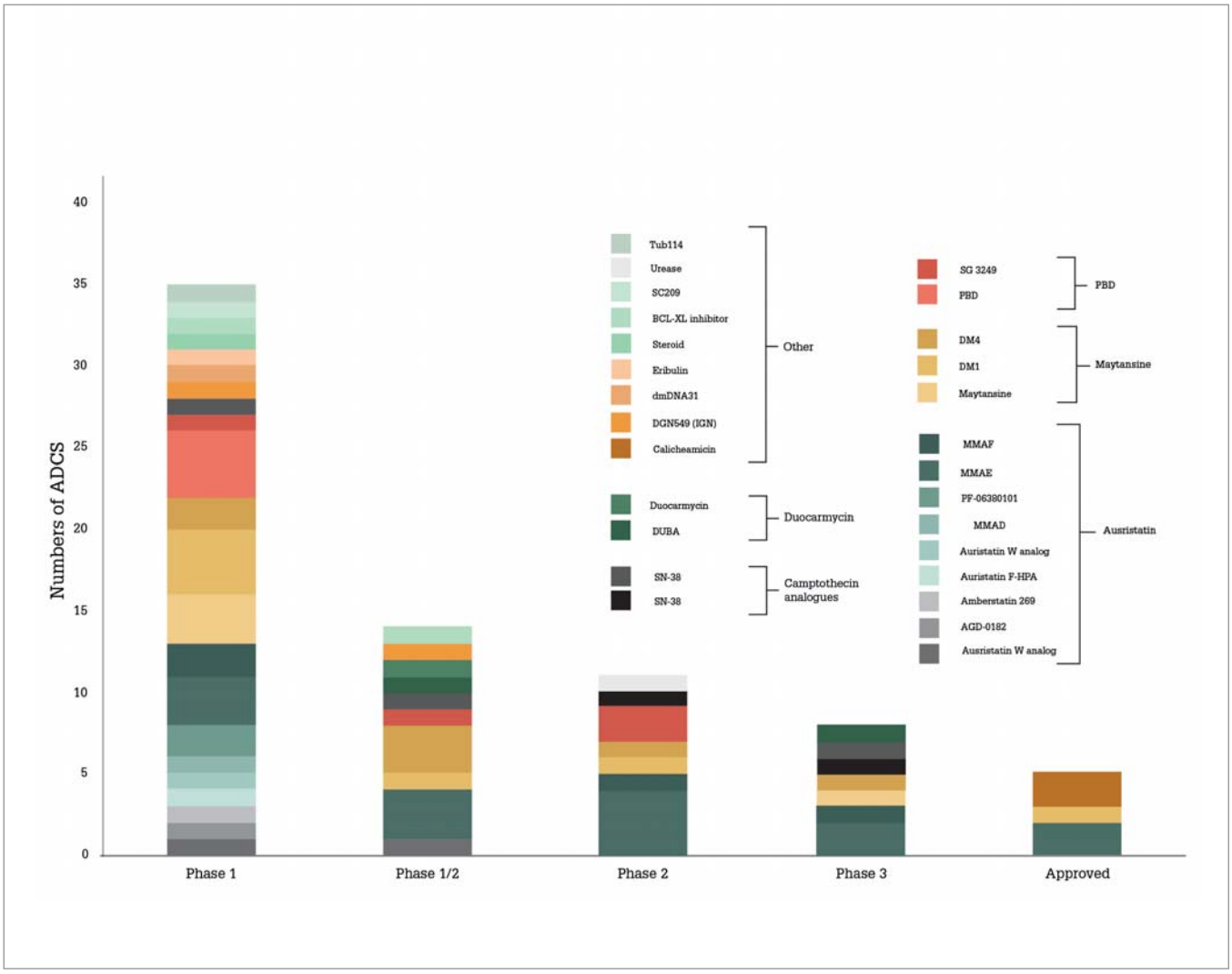


Figure 3: All disclosed payloads in the ADC clinic, segmented by payload type and phase of highest development.

not yet clear whether this will result in an improved therapeutic window.

The final hurdle

Once all three parts have been skillfully combined and the resulting ADC has demonstrated sufficient clinical efficacy, a manageable toxicity profile and a fit-for-purpose manufacturing process, the next hurdle is getting it over the regulatory line. The current phase III pipeline is one with potential; at least nine ADCs are now in the pivotal stage of clinical development, with at least four anticipating a biologics licence application submission by the end of this year.

Even though there are a diverse set of approaches, alternative conjugation methods and a cocktail of payloads to conjugate with, a priori design of the ideal ADC for a given target remains elusive to date. There is still some work to be done. But, with five approved ADCs and several nearing approval, success rates seem to be at least on par with other novel oncology drug classes.

The story of ADCs has proven to be one of tenacity and of pushing drug development boundaries through irrefutable innovation. The field is now maturing at an impressive rate with a burst of collaboration and investment and a healthy clinical pipeline. Is the next multi-million dollar deal on the horizon?

Data cut off date: September 2019.
Letrishka Anthony is a Principal Scientific Researcher at Beacon Targeted Therapies, Hanson Wade.

Next Generation Bioprocessing and the Implications for Viral Safety

With many companies embracing the move to next generation biopocessing, it is important that they do not forget to re-examine their approach to viral safety

By Kathy Remington, Ph.D, and Michael Phillips, Ph.D

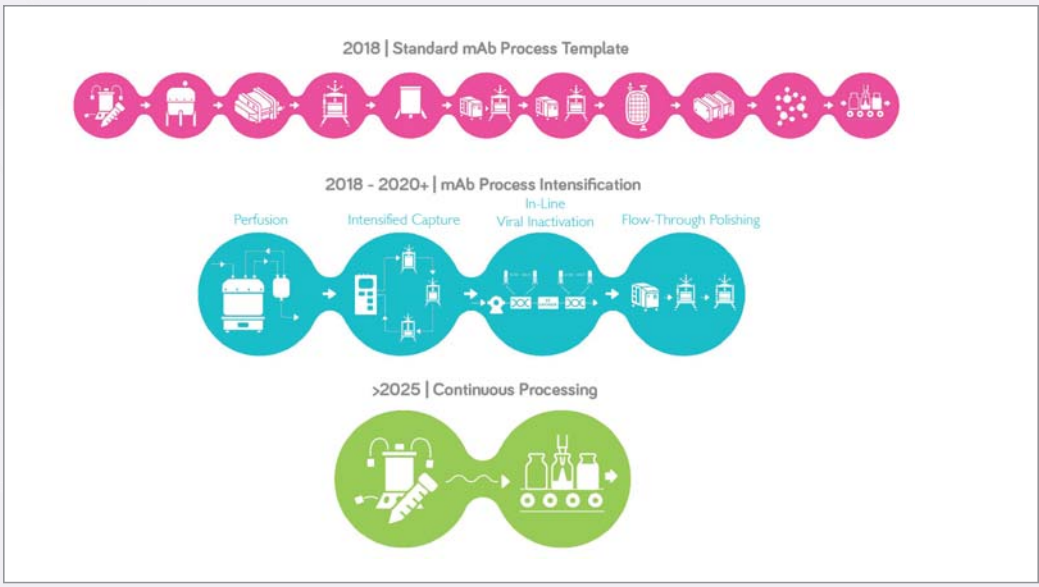


Figure 1: Viral safety strategies need to be re- examined as the mAb production template evolves to next generation bioprocessing.

Biomanufacturers are heralding next generation bioprocessing as a way to improve efficiency and productivity, reduce plant footprint and operating costs while maintaining the highest quality standards for the therapies being produced. Compared to traditional batch processing, this new manufacturing paradigm may include higher concentration fluids, higher mass loading of individual unit operations, longer duration processes and connected or continuous processes.

However, maximizing the benefits of this new approach to manufacturing requires consideration of the entire process from a holistic perspective. For example, process intensification using perfusion methodologies results in high density cell cultures that maximize protein productivity in relatively small bioreactors. While this can compress upstream timelines and increase protein yields per unit volume from the bioreactor, downstream operations may struggle to keep pace with higher titers from improved upstream operations.

It is clear that from a process development perspective, we need to consider the implications of efficiency improvements in a single operation in the context of the overall process. Overlaid on this, we may need to rethink how these changes might impact viral safety and how we assess the clearance capabilities of the individual operations.

Viral safety considerations with intensified processing

Higher concentration process intermediates, higher mass loadings on individual operations, longer duration processing, and connected or continuous processing all have the potential to impact viral safety.

- Higher concentration processing.
  High protein concentrations could impact virus inactivation – either through changing the buffering conditions for low pH virus inactivation or potentially interfering with viral inactivation using detergents. In the latter case, as long as the concentration of detergent or solvent/detergent is maintained, the higher protein concentration is less likely to impact inactivation.
  Highly concentrated loads may impact the performance of chromatography and filtration steps. Whether the chromatography step is run in bind and elute or flow-through mode, and regardless of the type of resin or membrane, the higher concentration of process intermediate, and potentially impurities, could influence the efficiency of the chromatographic separation. Viral clearance across the step may also be impacted through non-specific interactions of virus with the high concentration intermediate and the chromatographic resin, which may result in more virus binding to the intermediate or resin and consequently lower viral clearance. Similarly, higher concentration intermediates may impact virus filtration, necessitating increased use of prefilters to remove protein aggregates, or additional filtration membrane area. To confirm viral safety targets are met across downstream unit operations, viral clearance studies should be performed with higher concentration load solutions.
- Higher mass loadings.
  With intensified processing, a major goal is to identify technologies that offer high productivity, processing the same amount of mass through much smaller devices. For the most part, downstream processing of higher concentrations is advantageous, resulting in smaller intermediate product hold tanks, decreased loading times onto chromatography resins, and potentially higher effective capacities during chromatographic operations

– all key advantages of the approach. The biggest concerns would be potential competitive binding, which could reduce separation efficiency, and potentially introduce issues with protein stability. Chromatography resins and membranes for intensified processes should be capable of operating at high mass loadings while maintaining the expected separation resolution. For virus filtration, high mass loading of high concentration feeds could require more membrane area, unless the capacity of the virus filter can be increased. In addition, mimicking the at-scale process in a clearance evaluation would require a significant mass of product for small scale tests, and there is a higher likelihood that the virus spike itself might interact with the high concentration feed, which could, in turn, affect the filterability of the process solution.

- Longer duration processing. Intensified processing may involve targeting the same mass loading, but operating at lower flux for a longer duration. Depending on process duration, this is generally not expected to impact viral safety. Clearance evaluations would need to mimic this scenario, and include several starts/stops or process interruptions to mimic likely processing conditions. In addition, after several days of processing, bioburden could be a concern so manufacturers may need to think differently about bioburden control.
- Connected/continuous processing. Adoption of this strategy may have the biggest impact on viral clearance assessments as there will most likely be two unit operations running simultaneously both of which are designed to remove virus; for example, anion exchange chromatography and virus filtration. During a standard batch process, it is easy to isolate process steps and evaluate the viral clearance potential of each step independently. For a continuous process, it is more difficult to isolate each step, and instead of assessing clearance of a homogeneous batch, clearance would be evaluated across a step where the load solution might have a different composition at the start and the end of the 'batch'. Additionally, evaluation of viral clearance will require specialized techniques and equipment.

Importantly, if an existing process for which viral clearance data have previously been generated is modified and intensified, that clearance data may no longer be valid. The increased concentration of the process intermediate, adjusted loadings on individual unit operations and slight modifications to the unit operation process window may impact the levels of viral clearance that can be achieved for individual steps. To assure the new process can deliver the expected level of viral safety, clearance studies should be performed using the new, more concentrated intermediate under the new process conditions.

Evolving the approach to viral safety

It is clear that next generation bioprocessing strategies impact the approach to viral safety. By connecting process steps, we can no longer evaluate the viral clearance of isolated steps, and process development should ideally include viral clearance evaluations. In addition, unit operations may be impacted by the previous step and the load solution to a step may not be homogeneous. This will require a creative approach to modeling newly developed processes to ensure they accurately represent the manufacturing operations. Furthermore, how we execute virus spiking studies may need to be re-evaluated to minimize any negative impact of addition of virus to the test system.

At Merck, we are focused on enabling advanced manufacturing through our BioContinuum™ Platform strategy that includes new process technologies and systems combined with new digital solutions. From a process technologies and systems perspective, we are developing solutions to support intensified fed-batch and perfusion processes, intensified capture, in-line viral inactivation, integrated flow through polishing, and continuous ultrafiltration/diafiltration. From a digital perspective, we are developing a new control platform and orchestration platforms that would be 'future-ready' to support additional digital technologies required to enable advanced manufacturing.

The way forward

From a viral safety perspective, monoclonal antibodies and recombinant proteins have a very safe track record. Although we may feel confident that next generation approaches are similarly safe, we need to demonstrate that intensified and continuous processes deliver the expected levels of viral safety. Doing this with confidence will require creativity in the development of novel spiking strategies and accurate small-scale models that reflect new processing conditions.

Undoubtedly, intensified processing requires the biopharmaceutical industry to think differently and more holistically. The ultimate benefits of the adoption of next generation approaches, however, far outweigh any challenges presented by technical, regulatory, and implementation aspects.

Kathy Remington is a Technical Consultant focusing on the BioReliance® portfolio, and Michael Phillips is Director of Next Generation Bioprocessing R&D, both at Merck.

The life science business of Merck operates as MilliporeSigma in the US and Canada.

Welcoming Change

Sitting Down With… Tony Hitchcock,
Technical Director, Cobra Biologics, Keele, UK.

If you hadn't pursued a career in biopharma, what would you be doing now?

I think I would have always found my feet in a science-based career. I always had a natural affinity for science subjects in school – as did my identical twin brother. My brother now works in microbiology and pathology, and people still sometimes confuse us! As part of my sandwich year placement during my degree, I worked at a distillery, which made me consider a career in the brewery industry as a microbiologist, ultimately though I chose pharma.

How did you come to join Cobra Biologics?

Cobra was founded by Roger Craig to pursue the development of novel gene therapies. At the time, I was working at ICI Pharmaceuticals (later becoming AstraZeneca's site at Alderley Park in the UK) in a department focused on developing recombinant protein therapies. Unconvinced of the potential of biotech products, ICI/Zeneca pulled the plug on these programs, which prompted me to join Roger at Cobra. Initially Cobra only had three or four employees – a stark contrast to the thousands who worked for ICI/Zeneca – which was a shock to the system, but also a source of motivation for my colleagues and I. We wanted to prove that we could take the concept of gene therapies and make them a clinical reality, and in many ways we were naive of the challenges. Of course, there have been ups and downs – we experienced significant growth in the 1990s and completed the biggest round of fundraising for a biotech company in the UK at the time, but the 2000s saw difficult times for the gene therapy field, with limited funds and belief in this approach. Today, the gene therapy market is very buoyant, allowing Cobra to expand, and we now have 200 employees across our sites in the UK and Sweden.

What are your proudest moments?

The backbone of our business has always been our plasmid DNA production platform – after all, we've been working on it for over 20 years. It has proven to be effective in allowing us to support a broad range of gene therapy companies with the development of plasmids and viral vector therapeutics. As an extension of this, we have been involved in the development of two licensed gene products. It's one thing to have an idea and concept, but to actually be able to transform that into a commercially viable clinical product and make a difference to patients' lives is incredibly rewarding.

What big changes have you seen over your career?

I think the changes to regulatory requirements and expectations around the production of investigational products have had the biggest impact, and whilst this has presented challenges, I think it has really helped to move the industry in the right direction. The development of single use technologies has also had a massive impact on the industry, especially around the production of clinical materials. These technologies have changed the way companies approach drug development and manufacture. In reality, I don't think that many of the novel products we see today, especially in the area of advanced therapies, would have been possible to produce without single use.

Another big change I've seen in the industry is the growth of SMEs and, following on from this, CMOs, which comes down to greater access to scientific papers and knowledge. There used to be a feeling that you couldn't get into the industry unless you were a big player and had not just the funding, but also the knowledge base to support the production of novel therapeutics. Once the internet made academic information available to all, it helped SMEs develop and become innovators in the field. This, in turn, spurred the growth of CMOs with the need for manufacturing, including the use of under-utilized manufacturing facilities, as was the case with Cobra, which developed manufacturing capabilities when the company was first founded.

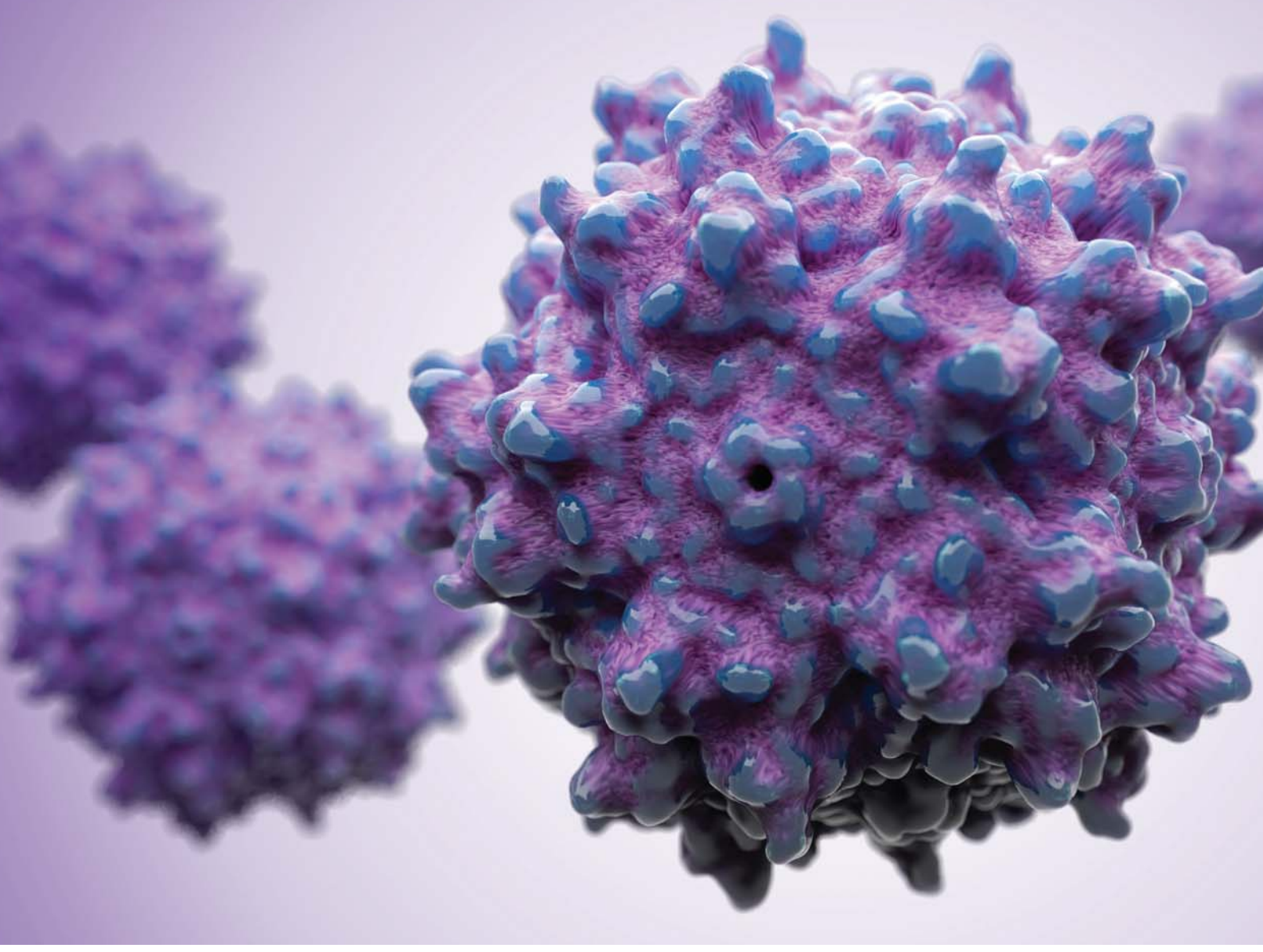
What areas would you like to see the industry improve upon?

Whilst those involved in pharmaceuticals see an industry based around a large number of very talented individuals, working to develop new and improved medicines that improve a patient's quality of life, my view is that the external perception is often very different. In reality, the public still has little, if any, understanding of what pharma does and how it is of benefit to them, which is not always helped by some of the industry's own behavior at times. This inevitably creates some negative perceptions of the industry, which holds people back from wanting to pursue careers in it.

By getting involved in STEM outreach programs and events run by local organizations – which I find highly rewarding – it is very apparent to me that many young people aren't aware of the career opportunities that exist for them in the field. To them, the only science-based careers available are in medicine or healthcare. As an industry, we all need to do better at communicating what we are all about and how gratifying careers in pharma can be. If we learn how to sell our message to the public, I believe we will see the number of graduates interested in professional careers in the industry increase.

Have any other industry trends caught your eye?

The industry went through a phase where everything was about antibodies, but now we are seeing the re-emergence of novel therapeutic areas and approaches, such as microbiome-based therapeutics – which I find a fascinating field. Throughout my career, I've been responsible for making other products such as phages, which are being used as microbiome-based products. The potential for this field is huge, but there are some challenges the industry will need to address to make these new products – which may require new technologies. However, it is incredibly exciting to have new approaches to treat diseases.



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