WorldPharma

World Pharmaceutical Frontiers

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Put the patient first

Why user engagement pays off

A more sustainable future

How pharma is going green

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Outsourcing

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A closer look

It's a difficult time for pharma. The *BMJ* has just published a paper indicating that half of all cancer drug trials are biased. An op-ed by UC Hastings law professor Robin Feldman in the *Washington Post* argued that pharmaceutical investment in cancer over the past decade has not paid off.

Meanwhile, there are worldwide attempts to cap drug pricing. In the US, The Lower Drug Costs Now Act has been introduced to the House of Representatives, which aims to save the US Government over $100 billion over 10 years. In the UK, the Labour party has announced plans to create a new publicly owned generic drugs manufacturer to supply drugs to the NHS if the party gets into government.

There are also pressures from inside the industry. The growing trend for personalised medicines is not only shifting the paradigm of healthcare delivery but also changing the way in which research and development is conducted. These drugs require companion diagnostics and genetic testing, demanding larger participant numbers and higher costs. However, the current regulations do not permit the collection of large amounts of data on patient populations and private healthcare systems often do not have the infrastructure to be able to collect this information either. This results in more difficulty in getting these medicines approved – and lower profit margins.

Despite these challenges, there are reasons to be optimistic in pharma, many of which we explore in this issue. We find out how embracing patient-centricity in drug delivery offers benefits for industry and patients alike on page 70; investigate the advantages of the implementation of novel technologies, such as 3D printing, on page 63; and dive into the ways that strategic sourcing and management of supplier relationships can enhance sustainability on page 18.

With no signs of pressures easing up anytime soon, it is clear that a more collaborative approach is needed, with pharma companies working more closely with both contract manufacturers and patients. This helps to streamline processes to make manufacturing more efficient and creates products that are more patient-centric with less of a negative impact on the environment.

Perhaps the benefits of collaboration can best be summed up by Helen Keller, US author, political activist and lecturer, who said, "Alone we can do so little; together we can do so much."

Emma Green, editor

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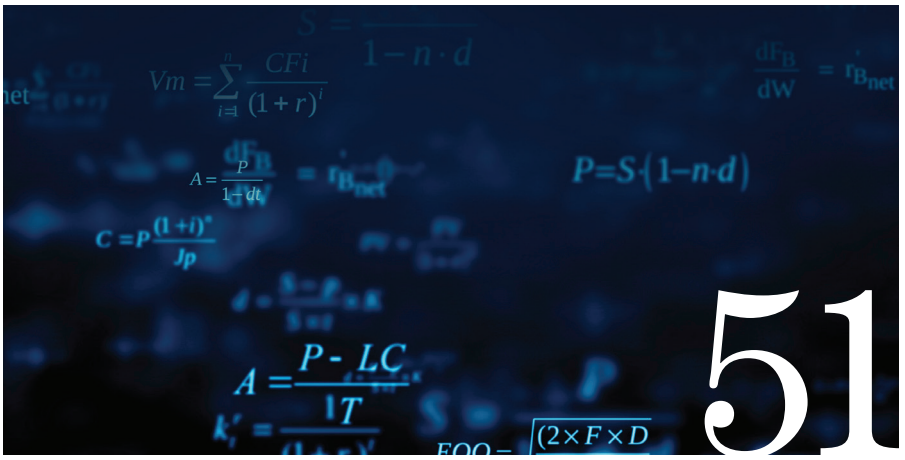

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"The future of pharma is about embracing technology and a much broader definition of medicines."

Paul Tunnah, founder and CEO of Pharmaphorum

Sanofi and Google to set up healthcare innovation lab

Sanofi and Google are set to establish a virtual innovation lab to tap emerging data technologies as part of a new project. Both companies will use digital technologies to better understand key diseases and extract-related patient insights, allowing Sanofi to develop more personalised treatments.

The innovation lab is expected to help transform the delivery of future medicines through improving the understanding of disease, operational efficiencies, and the experience of Sanofi's patients and customers. Sanofi's database will be used to understand which treatments work best for patients.

Sanofi and Google intend to use AI across data sets to forecast sales, informing marketing and supply chain efforts. By using these analytical tools, the companies will be able to take into account real-time information, including geographic, logistic and manufacturing constraints to help optimise the accuracy of their predictions.

"We stand on the forefront of a new age for biology and human health, with the opportunity to transform healthcare through partnerships with pioneering technology and analytics companies," said Ameet Nathwani, Sanofi's chief digital officer, chief medical officer and executive vice-president, medical. "Combining Sanofi's biologic innovations and scientific data with Google's industry-leading capabilities, from cloud computing to state-of-the-art artificial intelligence, we aspire to give people more control over their health and accelerate the discovery of new therapies."

Cancer drug data set to power the next wave of therapeutic discovery

The Genomics of Drug Sensitivity in Cancer project recently, released the results of four years of intense data gathering and exploration, which will power genetic research into cancer treatment worldwide. The freely available data includes unique data comparing almost 1,000 cancer cell lines' responses to 453 licensed and experimental drugs.

The project, led by researchers at the Wellcome Sanger Institute and Massachusetts General Hospital, builds on the previous six years' study and almost doubles the volume of novel data available on the website – making it the largest public data set of its kind in the world.

This data release brings the amount of freely available, open-access data on the website to 453 cancer treatment compounds, 989 cancer cell lines, 494,973 genomic associations tested and 386,293 drug dose response curves.

The Genomics of Drug Sensitivity in Cancer project is a pioneering public-private partnership funded by Wellcome. It combines samples of hospital patients' cancer cell lines with licensed and experimental cancer drugs from a number of pharmaceutical companies, and applies in-depth observation and genetic analysis to identify how the underlying changes in a person's DNA affect how they will respond to treatment. The ultimate goal is to identify biomarkers that could be used in the clinic to indicate which drugs will work best to treat a patient's cancer, based on the tumour's genetic profile.

Europe needs to adapt faster to gene therapy challenges

Europe's leading nations should commit to a rapid overhaul of health technology assessment (HTA) and bold initiatives such as new pan-European real-world evidence (RWE) frameworks, to support cell and gene therapy revolution in the region, according to a recent report from The Alliance for Regenerative Medicine (ARM).

The international advocacy organisation representing cell and gene therapy companies, and the broader field of advanced therapy medicinal products (ATMPs) has more than 70 members across 15 countries in Europe and is working closely with European stakeholders, looking to create a leading commercial and regulatory environment for ATMPs in the region.

Global opportunity to reduce antibiotic waste

Experts from across the globe are calling for a 'One Health' approach to combatting antimicrobial resistance (AMR) and for recognition of the impact that antibiotic production has on the environment.

"Alongside antibiotic stewardship and infection control we need to see regulation regarding emissions into our rivers," said Professor William Gaze, a microbial ecologist who studies antimicrobial resistance at the University of Exeter in the UK. There are three principles in the fight against AMR:

- Take antibiotics only when needed (by patients) and exactly as prescribed.
- Make antibiotics in a sustainable way by adopting emission targets (by manufacturers).
- Buy antibiotics only from responsible sources to ensure a clean supply chain (by procurers).

In a recent report by the Access to Medicine Foundation, only 15 of the largest pharmaceutical manufacturers were highlighted as having some form of an environmental risk management strategy that aimed to minimise the impact of antibiotics discharged from manufacturing processes. However, only eight of these companies have already set limits on antibiotic discharge in waste waters.

Distributors in the pharma chain

Five major trends impacting distributors in the pharma industry

1. **Consolidation and integration**
2. **Emergence of personalised care**
3. **Advances in technology**
4. **Non-traditional competitors**
5. **Public scrutiny**

In the US:

180 million
Patients regularly take a prescription medication.

231
The average number of recall events processed annually by each distributor.

1,300
Manufacturers are served by distributors.

83%
Customers receive deliveries of prescription drugs five times per week or more .

22,000+
Independent pharmacies are supported by distributors' core and value-added services.

180,000+
Dispensation points are supplied by distributors whose customers include pharmacies, larger retail outlets, hospitals and GPs.

11.3 million
Prescription units are purchased from distributors each day.

Source: Deloitte and Healthcare Distribution Alliance 2019, 'The role of distributors in the US healthcare industry'

Ride the wave

The ability to share data throughout the entire supply chain is essential to optimise logistical services for pharmaceutical products. To achieve this goal, the implementation of digital technologies plays a key role. Emma Green speaks to **Niels Hackius**, research associate at the Hamburg University of Technology, about the range of tools available, particularly the value of blockchain.

Talk of blockchain is omnipresent. Invented by Satoshi Nakamoto, it remained relatively underground until a number of large companies joined forces to build a blockchain-based platform for financial services.

It has taken longer for other industries to embrace the technology, not least the pharmaceutical industry due to its highly regulated environment. Nevertheless, there is a rising awareness of the value that blockchain and other related tools add to the supply chain and logistics.

Niels Hackius, research associate at the Hamburg University of Technology, became increasingly interested in the topic after asking a question on the subject as part of a larger research project on supply chain and logistics. The finding that "nobody knows what blockchain is" led Hackius to convince other professors to look more closely at blockchain and its capabilities.

Although describing exactly what blockchain is remains a challenge, its role is simple to grasp.

"It is a tool that forces you to do one thing and that is to get your processes straight," says Hackius. "Once you have that you can do so many nice things."

One of these is the collection of large amounts of data, such as through the use of sensors. "When you attach sensors to things, the information becomes easier to handle and cheaper," says Hackius. "Also, you're able to process more data and that is a big topic."

It is, of course, imperative to have tools to adequately analyse this data, an area often referred to as artificial intelligence; however, Hackius is reluctant to use this term. "We call this machine learning or data analytics because there is nothing intelligent about it," says Hackius. "There is no brain that we are growing here that you can use."

Nevertheless, this process is invaluable in providing new insights for the supply chain and logistics. "Companies are coming to realise that you can make predictions from your data and this can be really

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useful," says Hackius. "It's not that they haven't done this before, but I think the realisation that you can do it and you should do it is now much bigger."

Despite the benefits, there can be a reluctance to implement these technologies because of the risks involved. "This makes sense because you don't want to damage some kind of raw material or product," says Hackius. "You don't want to be the guy that says 'I tried a new technology and it didn't work out.'"

The barrier to blockchain

The pharmaceutical industry is often criticised for being behind other industries when it comes to implementing blockchain and related tools. This is not uniformly the case, however. "Pharma want to have items that are very trackable," says Hackius. "They are willing to spend more money on ensuring that their goods are handled correctly, which can be an advantage compared with industries that don't have that money to spend. That's why blockchain is so fascinating because it has such a large sink for data that can be tracked."

The huge potential of these tools is clear but there are also a number of challenges with incorporating them into supply chain and logistics processes. "In terms of digital technologies more generally, it is difficult to do," says Hackius. "It's hard to get a system that has been working for years, even decades maybe, to move to a new standard. People working in the field are faced with the physical product that is affected and might be incredibly difficult to get back on track if something fails."

Ensuring that there is adequate data that can be analysed is also key. "You need to make sure that every step is recorded," says Hackius. "In general, I think it is just hard to do and comes with a huge perceived risk versus the benefits that you can get from the analytics."

The culture of supply chain and logistics can also present a barrier to innovation. "My impression is that the logistics sector and the supply chain is not particularly attractive for young people, so it is hard to get people that have these radical ideas," says Hackius. "If you have people that think that everything is fine then you are stuck."

The need for speed is another pressing issue. "In Germany at least, the mentality is 'we will work out the perfect solution first in our lab and then maybe we will try it'," explains Hackius. "Then, before you have this solution, the world has moved on."

That is why looking at companies moving quickly in this space can be so valuable. "Amazon is a good example of a company that isn't afraid to make mistakes," says Hackius. "It has recently set up a logistics service in Hamburg and it is terrible. But everyone knows that in three years it will be better than any other service. They can just throw loads of money at it and build everything from scratch."

In addition to these observations, working more strategically with other companies can be hugely beneficial. "With blockchain, you need to work together with multiple companies," explains Hackius. "There is no real big working example where you can see that companies have done this and seen a benefit from it. Everyone is sitting there thinking 'I'll wait and see.'"

One of the obstacles with this collaborative approach is the issue of privacy. "When you make processes transparent, they become visible to new players," says Hackius. "When companies work together on a common blockchain platform, they fear that they are not as competitive and they may be concerned that other companies might see their customers and approach them."

There are a few examples of companies working together successfully; for example, the Pistoia Alliance, a not-for-profit members' organisation working to lower barriers for innovation in healthcare R&D through pre-competitive collaboration. The Alliance was

100

The Pistoia Alliance, a not-for-profit member's organisation, has grown to 100 members worldwide since 2007.

Pistoia Alliance

Key characteristics of blockchain

- **Decentralisation:** in conventional centralised transaction systems, each transaction needs to be validated through the central trusted agency (for example, the central bank), inevitably resulting in the cost and the performance bottlenecks at the central servers. However, a transaction in the blockchain network can be conducted between any two peers (P2P) without authentication by the central agency. In this manner, blockchain can significantly reduce the server costs (including the development cost and the operation cost) and mitigate the performance bottlenecks at the central server.
- **Persistency:** since each of the transactions spreading across the network needs to be confirmed and recorded in blocks distributed across the whole network, it is nearly impossible to tamper with. Additionally, each broadcasted block would be validated by other nodes and transactions would be checked. Therefore, any falsification could be detected easily.
- **Anonymity:** each user can interact with the blockchain network with a generated address. Furthermore, a user could generate many addresses to avoid identity exposure. There is no longer any central party keeping users' private information. This mechanism preserves a certain amount of privacy on the transactions included in the blockchain.
- **Auditability:** since each of the transactions on the blockchain is validated and recorded with a timestamp, users can easily verify and trace the previous records through accessing any node in the distributed network. In itcoin blockchain, each transaction could be traced to previous transactions iteratively. It improves the traceability and the transparency of the data stored in the blockchain.

Source: Strategy and PricewaterhouseCooper

conceived in 2007 and has since grown to over 100 members worldwide. It emerged from the realisation that real progress in implementing digital technologies cannot be achieved on its own and instead fosters collaboration between organisations of all sizes to drive change forward.

Make the jump

In light of the rapid pace of technological development, making predictions is no easy feat. As a result of speaking to a range of industry professionals currently implementing tools like blockchain, Hackius is excited about the future of supply chain and logistics. "Over the long term, robots, wearables and self-driving trucks are coming," says Hackius. "The robots, in logistics at least, are going to be a big deal but the issue is that they are not cheap enough and they cannot do certain things, which is currently being researched."

One particular deficit of robots is the inability to grip items similarly to a human hand. "When you lift something, you immediately know how hard you can squeeze," says Hackius. "As far as I know, there is no machine that can differentiate without extensive learning processes. If you figure out the hand, you are going to be very successful."

In order to fully realise the potential of these technologies for the supply chain and logistics, it is essential for companies to take a leap of faith. "At some point they will have to make the jump and say 'we'll implement a completely new IT system' and we'll also open up to make things accessible for outside partners or other people will do it," says Hackius. "You need to invest a lot to make that happen, so it is kind of a chicken and egg problem."

The pharmaceutical industry will certainly not change overnight; however, change will happen in a tangible way. "The main thing that we will see is more data being generated because it is easier," says Hackius. "They can then do data analytics and the little wins will drive progress forward making things better. Small data points that you previously didn't have access to can be hugely helpful for the supply chain."

There is huge potential for the use of blockchain in the pharmaceutical industry to track data.

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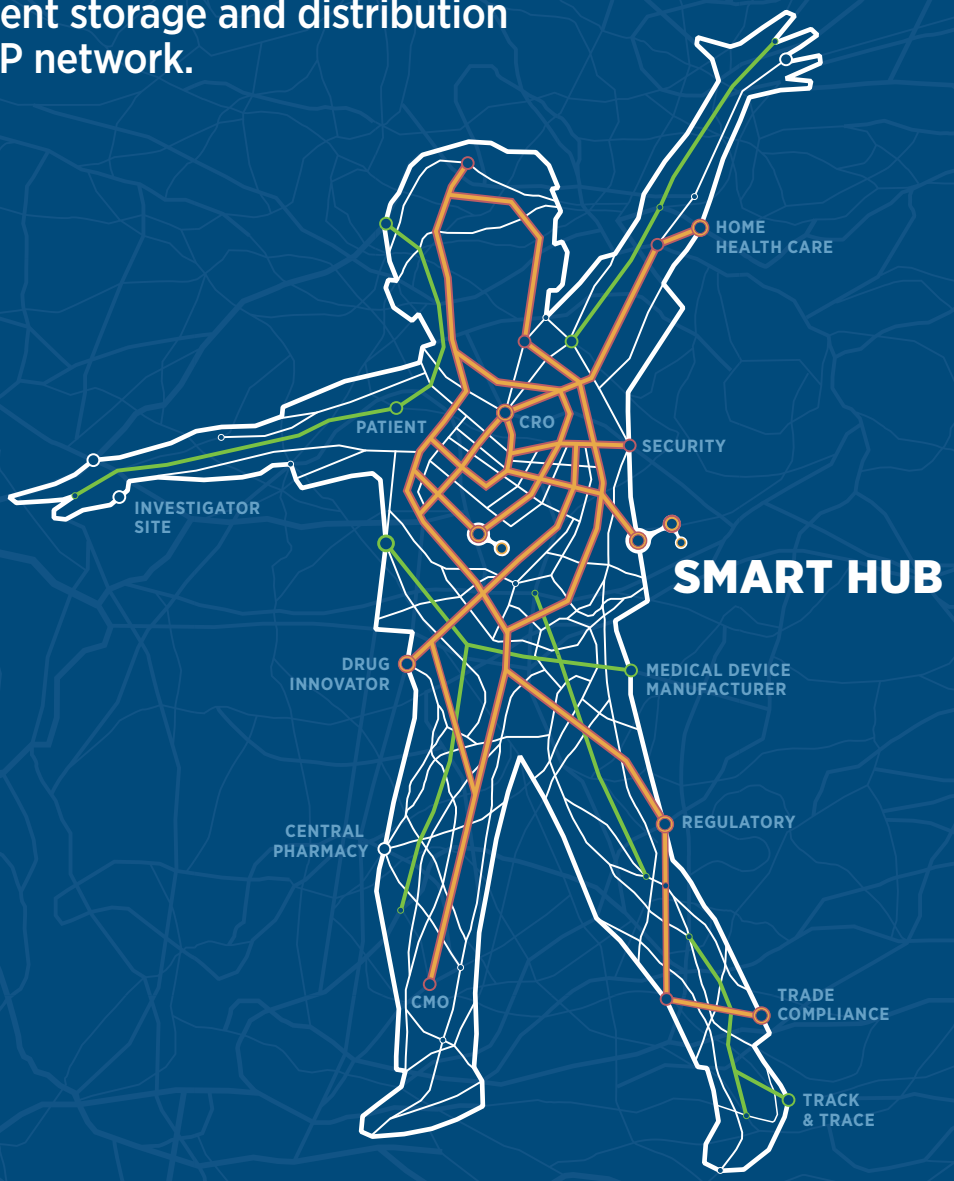

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Storage and distribution support for clinical trials worldwide

Patient centricity has moved to the forefront of clinical trials. Direct-to-patient (DTP) services provide convenience, and lead to greater participation and retention, addressing two key challenges that face study sponsors. **Yourway** has the resources and expertise to devise tailored clinical logistics solutions for decentralised/virtual trials anywhere in the world, for even the most sensitive medications. Gulam Jaffer, president of the company, discusses the logistics of supporting DTP trial models.

Many of the drug candidates advancing through the clinic, such as next-generation antibodies, cell and gene therapies, and other specialised and targeted therapies, are very different from drugs developed even a decade ago.

In 2018, nearly 40% of drugs in the pharmaceutical industry pipeline were biologics, most of which require storage and transport at low temperatures. A much greater proportion of pharmaceuticals treat rare diseases that affect small patient populations – many of which are developed by small or emerging pharma and biotech companies. The result of these trends is a significantly larger number of clinical trials, often with less centralised sites located in multiple countries.

Yourway's integrated packaging and shipping services mean that the decisions about packaging design are made with comprehensive understanding of the conditions that the shipment will encounter.

Evolving challenges of clinical trials

Efficiently and effectively managing the supply of speciality clinical materials and patient samples used in international trials has become more challenging. Navigating varying and rapidly evolving complex and stringent regulations in each country requires detailed knowledge. Compliance with data protection laws, which are also rapidly changing and vary among regions, is complicated, as is ensuring data security and protection against digital attacks. Access to advanced packaging solutions that provide active temperature management combined with real-time tracking capabilities has become essential.

The two biggest challenges are patient recruitment and retention. A 2012 study estimated that more than 60% of trials fail to fully enrol their intended participants and approximately 30% of patients drop out of the studies.

"DTP services include delivery and administration of clinical trial drugs to participants in their homes, as well as pickup of patient samples."

The consequences are significant. Nearly 80% of clinical trials do not finish on time, with 20% delayed for six months or more. For a blockbuster drug, each day a trial is delayed causes a loss in revenue of roughly $8 million. For orphan and other specialised therapies, the loss in revenue opportunity is approximately $600,000 per day of delay.

Direct-to-patient solutions

Patient centricity has thus moved to the forefront, with trial protocols focused on patient convenience and incorporating patient input. It is also driving the adoption of DTP services in virtual clinical trials.

DTP services include delivery and administration of clinical trial drugs to participants in their homes, as well as pickup of patient samples, so patients can avoid travel and widely

DTP services include administration of clinical trial drugs, and warehousing and distribution support.

dispersed patient populations can participate in a single trial. DTP services are ideal for trials enrolling patients in remote locations or with mobility issues.

For sponsors, DTP services can boost participation and retention, and potentially lower trial costs. The ability to access real-time data from remote monitoring devices enables trending and more rapid identification of potential safety issues.

These benefits have been confirmed in various studies. For instance, one survey found that over half of patients indicated that they would be more likely to participate in a clinical trial if they could receive care at home. Another study found that the use of DTP services increased patient retention rates – with rates above 95% in some cases.

The move towards decentralised/virtual trials

Despite the limitations of virtual or decentralised trials, such as varying international regulations or the need for nursing assistance, approximately 24% of clinical studies conducted in 2017 included DTP services. A total of 30% of respondents in a 2017 study indicated that their companies were considering the incorporation of DTP services in trials over the next 12–18 months. The FDA, meanwhile, recently published a draft guidance on the use of electronic media to facilitate the informed consent process for clinical trials, and has endorsed DTP services and virtual clinical trials.

A solution-based approach

Partnering with a clinical logistics provider that has an established, global network of depots, demonstrated knowledge of the regulations in these regions, centralised management and tracking systems, and a highly trained workforce is the key for successful virtual clinical trials and DTP studies.

Yourway BioPharma Services offers – in addition to the comprehensive transport capabilities – comparator drug sourcing, primary and secondary pharmaceutical packaging services, warehousing and distribution support, unused product return services, and assistance with logistics project management for all types of clinical trials, including decentralised studies that rely heavily on DTP services.

As the only truly integrated premium courier and clinical packager in the market, Yourway is uniquely positioned to support DTP clinical trials. The ability to access packaging services and courier/shipping services from a single provider creates unique opportunities to find solutions that will protect the integrity of the drug products and increase the efficiency of the trials.

Understanding the full scope of a client's needs allows it to apply a solutions management approach to eliminate the inefficiencies that can result from a complicated supply chain involving multiple discrete service providers. Integrating packaging and shipping services at Yourway means that decisions about packaging design – from primary and secondary packaging through temperature-controlled shippers and beyond – are made with comprehensive understanding of the conditions that the shipment will encounter on the way to the patient. Likewise, routing, shipping, and temperature-controlled decisions are made with a unique and complete understanding of the capabilities of the clinical packaging.

Furthermore, because the relevant drug products and related materials remain in Yourway's hands from the initial packaging steps in the temperature-controlled packaging facilities, all the way through to the last mile to patients, it can ensure an unbroken temperature-controlled chain. It maximises the use of supplies, and minimises waste and shipping costs while ensuring that products stay within specifications (for example, temperature, pressure and vibration), creating efficient and effective solutions for even the most complex supply chains. Additionally, since no handoffs are required between packaging and shipping, we can eliminate lags and enhance the efficiency of the entire trial, which is critical given that all lost time can cause loss of profit.

Unlike the few big players in the clinical trial logistics space, Yourway offers highly personalised services that can only be found with small to mid-sized companies. It has the bandwidth of a large company but are responsive to the customers' individual needs in a way that only small companies can be. It offers true one-on-one customer service that ensures high-quality, responsive, tailored support from start to finish. ●

References available on request.

For further information

www.yourway.com

Simulations minimise risk

For over five years, **SmartCAE** has provided simulation solutions tailored to the field of temperature-controlled logistics. Its 'virtual cold chain' software products and services help pharmaceutical companies minimise lane risk and total cost of ownership (TCO). Managing director Stefan Braun explains the stark difference simulation can make to operations.

It is unavoidable, shrugs Stefan Braun: for all the refinement and beautification, car design eventually comes down to throwing hunks of metal and plastic into walls. The knack is knowing what will happen when you do.

As Braun puts it, "the nice thing for car manufacturers is the predictions from their virtual tests are so good that by the time they crash the first car, they can feel very secure that it will work."

Braun's pitch is that the virtual cold chain company, SmartCAE, can use rapid simulations to bring the same sense of security to shipping temperature-controlled pharmaceuticals. Given Braun's background in modelling climate control in cars, it is not surprising that the metaphors are drawn from the automotive industry, but they could just as easily be an example of the pharmaceuticals the company helps ship. In a world of multi-phased double and triple-blind clinical studies, it is surprising that so many companies are comfortable making decisions on the basis of putting a couple of different boxes on different aircraft.

The likelihood of risk

It is not that any of these companies are neglecting their responsibilities to patients and customers. Rather, as Braun explains, it is over-engineering its responses. As Braun sees it, putting the most expensive temperature-controlled box on the fastest, most tightly controlled airline pharmaceutical service because it is considered a lane high-risk is, "like driving a tank in London because you're worried about accidents".

"The problem at the moment," Braun continues, "is people don't see this because they have no data on it and they just think they have to do everything to get rid of risks. But how much are they paying? 100% more? 200% more? What is a fair value to accept for a little bit of risk?"

By providing that data for every possible lane – sourced worldwide from airlines, box vendors, logistics companies, weather stations and more – SmartCAE is able to account for far more of the parameters that impact the likelihood of excursions, then even the most extensive and intensive series of physical tests. Furthermore, as a single simulation takes two to five minutes and a climate chamber test can last for upwards of 80 hours, it is possible to rapidly run thousands of virtual tests to account for every variable and possibility.

"In reality there is not one profile of what happens to your box," explains Braun. "If you ship it from London to Sydney, you have different modes of transportation, different times of the day, you have sun or no sun: you have a lot of different things and by running thousands of possible scenarios you get a good idea of how robust a solution is."

With that, by giving companies an accurate accounting of the risks and costs associated with a particular combination of lane, box and logistics, SmartCAE makes it possible to optimise safety even as it helps lower the total cost of ownership. As Braun details, "If you have a 0.5% risk of an excursion, but covering that 0.5% costs more than you would have to spend to remediate it, then you can see what the best course of action is.

"You never have no risks. But my point is, you have to understand your risk. What often happens is pharma companies can't go to insurance companies, because insurance companies cannot take on risks they don't understand. But if you can show this in a transparent way, then you can go to an insurance company and get a fair offer."

Maximise the cold chain

The possibilities for savings and optimisation do not end there. With its live data sources, SmartCAE's virtual cold chain continually tracks risk across all lanes, and records when changes in flight times and climate necessitate physical test shipments or present opportunities for further optimisations or cost savings.

As Braun emphasises, cost savings that arise from properly leveraging data on lanes with good logistics make it possible to invest more in packaging where it is actually necessary. "You can decide to spend more because you saved so much on other lanes and your patients need this medicine. You can take a look at your total costs and invest more in a specific lane to tackle a rare disease. Maybe in the past you'd conclude you couldn't make that shipment because it was too expensive."

On the other side, "If you have really good logistics you can ship a cardboard box and reduce your carbon footprint. It makes no sense to have perfect logistics and to send a 500kg paratrooper when you can ship a 50kg cardboard box. If you look at carbon footprints, sometimes we are really struggling because everything is so over-engineered. People get the best containers and ship them with the world's best logistics, and they have no excursions. That's fine, that's great, but you emit thousands of kilograms of CO_2 for nothing."

Just as clinical trials are structured to minimise bias and deliver the most accurate, objective and replicable results possible, SmartCAE's virtual cold chain solution maximises visibility of the cold chain while minimising the impact of any one box or logistics provider's viewpoint might have on results.

"As we're not related to any box vendors or logistics companies, we do not need to sell any particular product, so we can say on a rational, transparent, scientific basis that logistics provider A on lane B with box C is the best combination.

"It's very important for our customers that our approach gives a transparent solution and not one that ensures one vendor gets most of the money. Our point is that you can find the solution to lower the total cost of ownership." ●

For further information

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Air transportation remains an important factor in the pharmaceutical industry, ensuring the delivery of temperature-sensitive cargo to different destinations. **Air Canada Cargo** plays an important role in the delivery of pharmaceuticals through its specifically catered shipping solutions.

This year, Air Canada Cargo began its journey towards IATA CEIV pharma certification, starting with specialised training for its team of employees throughout its global network. The next steps involve assessment – starting at the corporate HQ level, followed by key stations throughout the network.

The assessment phase is "essentially like peeling an onion", says cargo product and business development, AC Cool Chain SME Carolyn Van Vliet. "We're reviewing our organisation, product, processes, documentation, training and infrastructure. While it's important for us to acknowledge the areas where we are already strong, it's important to be aware of areas that require some adjustments and place focus on implementing enhancements for continuous improvement. Our focus is on the technology piece, as improved use of technology and faster access to data will lead to greater visibility, allowing us to measure our performance more accurately and improve our response times if/when needed."

At Toronto Pearson International Airport, a touchpoint for most of the pharmaceutical shipments handled by Air Canada Cargo, pharmaceutical shipments are handled at GTA dnata. Certified by IATA's Center of Excellence for Independent Validators in Pharmaceutical Logistics (CEIV Pharma) for its pharma-handling processes and facilities, GTA dnata is fully equipped for handling temperature-sensitive shipments in varying environments and utilises advanced monitoring technology.

"Our collaboration with GTA dnata reflects our commitment to evolving our pharmaceutical offering to match our customers' needs," says Van Vliet.

New addition to the family

As well as having QEP accreditation – recognition from active container manufacturer Envirotainer that ensures it meets the high standard of handling shipments – Air Canada Cargo will soon add the CSafe RAP temperature-controlled container to its AC Absolute product offering. Part of its AC Cool Chain family, the AC Absolute solution is designed for handling active temperature-controlled containers. AC Pharmacair, its sister solution, is suited for passively packaged pharma shipments.

Air Canada Cargo aims to ensure the awareness and adoption of standardisation within air transportation.

With AC Absolute and AC Pharmacair-certified stations across the world, Air Canada Cargo facilitates trade for pharmaceuticals between all six continents, handling shipments that are routed to transit through one of its hubs such as Toronto, Montreal or Vancouver, in addition to those originating in or destined to Canada.

"Shipments from Zurich destined to Latin America transit through Toronto, or from the US to Asia through Vancouver," says Van Vliet. "As Air Canada's network continues to expand globally, Cargo will continue to leverage the pharma supply chain."

Air Canada Cargo is a member and participates in IATA's Time & Temperature Working Group, which provides a neutral environment with strict governance rules, where stakeholders within the airfreight sector meet throughout the year to discuss global standards, regulations and best practices. The objective is to ensure awareness and adoption of standardisation among all industry stakeholders involved in air transportation.

"Air Canada Cargo also works actively with our customers and we welcome their honest feedback about our service," concludes Van Vliet. "Through these exchanges, we are made quickly aware of areas in need of improvement – and for future demands and opportunities. When it comes to supporting our logistic service provider customers, we have participated in and encouraged tripartite meetings, which include their end-user customers, to provide visibility to our processes and operations that sometimes even the LPSs may not be exposed to. We consider this to be a true collaborative approach." ●

For further information

www.aircanada.com/cargo/en

Top of the green chain

Pharmaceutical companies have long grappled with getting their supply chains in order, especially when it comes to keeping them sustainable. But between lax reporting and environmental scandals, supply chains have traditionally been decidedly ungreen. Andrea Valentino talks to **David McClintock** and **Camille Messer** of sustainability ratings company EcoVadis about how a new joint initiative could finally help the industry clean up – and how the latest technology is pushing it along.

Hyderabad was once known as the City of Lakes. No longer: most of the water has disappeared and what remains is a squalid cesspool. One of the causes can be seen by wandering the suburbs north of the town, where every street is lined by gasping funnels. Hyderabad is home to 50% of the Indian pharmaceutical industry and, spurred on by lax oversight, drugs companies have run wild. Pharmaceutical factories regularly dump heavy metals and solvents into the water system, an ecological catastrophe that washes up thousands of dead fish every month.

Hyderabad might be an intensely shocking example, but it is far from unique. For years, the pharmaceutical industry has struggled with sustainability, especially when it comes to partners lower down the supply chain. From the irresponsible dumping of waste to an overreliance on unrecycled plastics – used in an estimated 90% of pharmaceutical supply chains – getting drugs to the people who need them can be a frustratingly dirty experience.

But the situation is far from hopeless. By using greener ingredients and encouraging recycling policies, there is plenty pharmaceutical companies

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can do to be more sustainable. This is equally true when it comes to their supply chains. By combining new technology with old-fashioned teamwork, the pharmaceutical industry is transforming how it works with suppliers, saving money and improving reputations along the way.

Sustain the pressure

In one sense, outrages like Hyderabad are just the sharp edges of a wider problem. As the pharmaceutical industry becomes more globalised – and blockbuster drugs are being swapped for cheaper alternatives – companies are increasingly making and selling drugs in developing countries, where manufacturing costs are often 40% below those in the West. A fine example of this trend is Sanofi, the Paris-based conglomerate, which now works with 86,000 suppliers across 157 countries.

Yet the dash to cheaper overheads is far from easy. "Not everyone can pay what the American healthcare system pays for pharmaceuticals," explains David McClintock, the marketing director at EcoVadis, a sustainability ratings company. "Companies have to find a way to make drugs profitably by going into other markets. But if you're sourcing from different places, you're facing lots of unknowns." To put it bluntly, if pharmaceutical companies can generally trust their suppliers in Antwerp or Düsseldorf, Hyderabad and cities like it are another story.

These challenges are especially urgent now that medical technology is developing so fast. The latest biological medicines, for instance, need to be carefully stored in chilled environments if they are to survive the trip from factory to clinic. That means spending more on electricity and packaging, but also pushing companies to invest in sustainability along the supply chain. This pressure is especially fierce given the potential to save money. Using sustainable insulation on the cold chain can cut energy costs by up to 80% – nothing to sniff at considering the biological drugs market is expected to reach $394 billion by 2024.

At the same time, these technical shifts are stalked by increased regulation. If a pharmaceutical company wants to transport cold-chain medicines, for instance, it now has to abide by UN rules that dictate insulation performance and heat extraction rates. National bodies are doing similar work, at least in rich countries. In 2012, Sweden became the first country to stick environmental rules into contracts with pharmaceutical companies, while the Environmental Protection Agency lately banned companies from tipping hazardous waste pharmaceuticals down the drain.

Even if the long arm of the law fails to change big pharma, the boardroom probably can. As Camille Messer, a senior client manager at EcoVadis notes, there is significant "investor pressure" on companies to become more sustainable, especially as any slipups can ruin their hard-earned reputation.

Checks and balances

Given these demands, you might expect pharmaceutical companies to have long ago adopted rigorous sustainability checks. Yet even a few years back, the situation was dire. Suppliers regularly turned in sustainability questionnaires without evidence, and many were overwhelmed after receiving the same massive surveys from all their customers at once.

"By using greener ingredients and encouraging recycling policies, there is plenty pharmaceutical companies can do to be more sustainable."

The results of all this were often predictable, especially in developing countries. The case of Changsheng is typical. A few years back, the Chinese drug company was caught falsifying production records and mixing up batch numbers, a lapse that led to a $1.3 billion fine. The rot has sometimes spread to big multinationals. Speaking in 2017, one GSK boss recalled finding a "cottage industry" of spamming suppliers with mystifying questionnaires. Graft inevitably followed: Chinese police discovered Chinese executives at GSK had spent $489 million to illegally boost sales. Not that GSK is alone. Both Pfizer and Roche, among others, have been criticised for their shoddy supply chain practices.

These scandals – what McClintock calls companies "stubbing their toes" – seem to finally have nudged big pharma towards change. Bayer now has a code of conduct based on UN principles, while Sanofi has embarked on an ambitious auditing campaign. This is shadowed by several industry-wide plans, including the Pharmaceutical Supply Chain Initiative and Together For Sustainability. Another is the Responsible Health Initiative (RHI). Founded by GSK, Takeda and Teva, and run by EcoVadis, the scheme aims to help pharmaceutical companies sharpen their supply chains and ensure that they dump unscrupulous partners.

At the heart of the project is serious investigative work. After one of the pharmaceutical companies gives EcoVadis a list of suppliers, Messer and McClintock come up with relevant lists of sustainability questions. To avoid the confusion that made earlier checks so cumbersome, the surveys are tightly focused. As Messer puts it, "a company of 25 employees that has three trucks in Belgium would not have the same material

$489 million

Police discovered Chinese executives at GSK had spent millions to illegally boost sales.

Reuters

The pharmaceutical industry is changing its supply chain for a more sustainable future.

risk as a 2,000 employee chemical manufacturing business across Asia-Pacific." Thanks to the RHI, meanwhile, suppliers only need to fill in a single questionnaire. The information is then shared to all their buyers at once. Nor does the RHI let partners get away with fiddling the books: EcoVadis always demands proof of good practice from suppliers.

"Because the pharma industry is so regulated, they have this culture of being focused on compliance levels. I believe that those companies that work with us are really trying to go in the direction beyond compliance."

The questionnaires are hardly scattershot though. By focusing on 21 key criteria – think water consumption and energy efficiency – then coming up with comparative scorecards, EcoVadis and the RHI help pharmaceutical companies judge all their suppliers from a single vantage point. That, in turn, encourages sellers to work sustainably in the hope of winning new business. "It's a rich rating and the scorecard gives enough feedback that you can incentive it," says McClintock. He has a point, not least given everything companies have been doing to prod their partners along. Last year, for example, AstraZeneca announced its first 'Supplier Sustainability Award', while Takeda has just enrolled another 125 suppliers in the RHI.

For her part, Messer thinks brandishing the carrot over the stick has notable advantages for the pharmaceutical industry, especially when getting companies to go beyond the call of duty. "Because the pharma industry is so regulated, they have this culture of being focused on compliance levels. I believe that those companies that work with us are really trying to go in the direction beyond compliance."

Animal pharma

Certainly, companies are now keen to flap their sustainability credentials, and not just when it comes to liaising with suppliers. For example, GSK uses leftover packaging to make construction material for waterproof flooring. At Baddi, a Johnson & Johnson plant in the Himalayan foothills of India, plastic and paper waste is now sent to recyclers, and food waste is left for the neighbourhood pigs. This consciousness even extends to basic manufacturing materials. By the end of this year, Unilever hopes to source all its palm oil sustainably, and Johnson & Johnson works with Indonesian farmers in similar ways.

Technology is another focus and as in other corners of the pharmaceutical industry, big data is at the vanguard of these advances. For example, Merck now mixes statistics and machine learning to forecast its needs, while Pfizer has developed an app to keep an eye on suppliers. EcoVadis has similar plans for the RHI. Rather than painstakingly investigating each supplier and giving them a sustainability score, McClintock and his colleagues have started letting computers do the hard work.

"There is not a non-zero amount of work to onboard suppliers, and [clients] want to make the best selections possible. We can leverage our giant database, with all of the inherent risk data that we have accumulated, to go through their entire chain and give them a sort of topographical map of risk and opportunity, and tell them 'this is where your assessment efforts are best applied'."

This is all good news, though it might be too late to save the City of Lakes. Recent surveys suggest that the water around Hyderabad is still near the filthiest in India, and many crops are too polluted to eat. The Indian Government has begun to take a tougher stance, setting up a National Green Tribunal to punish rule breakers, but violations in the developing world continue. Hyderabad is a reminder of how easily disaster can strike and how quickly progress can be wrecked if the industry gets lazy. ●

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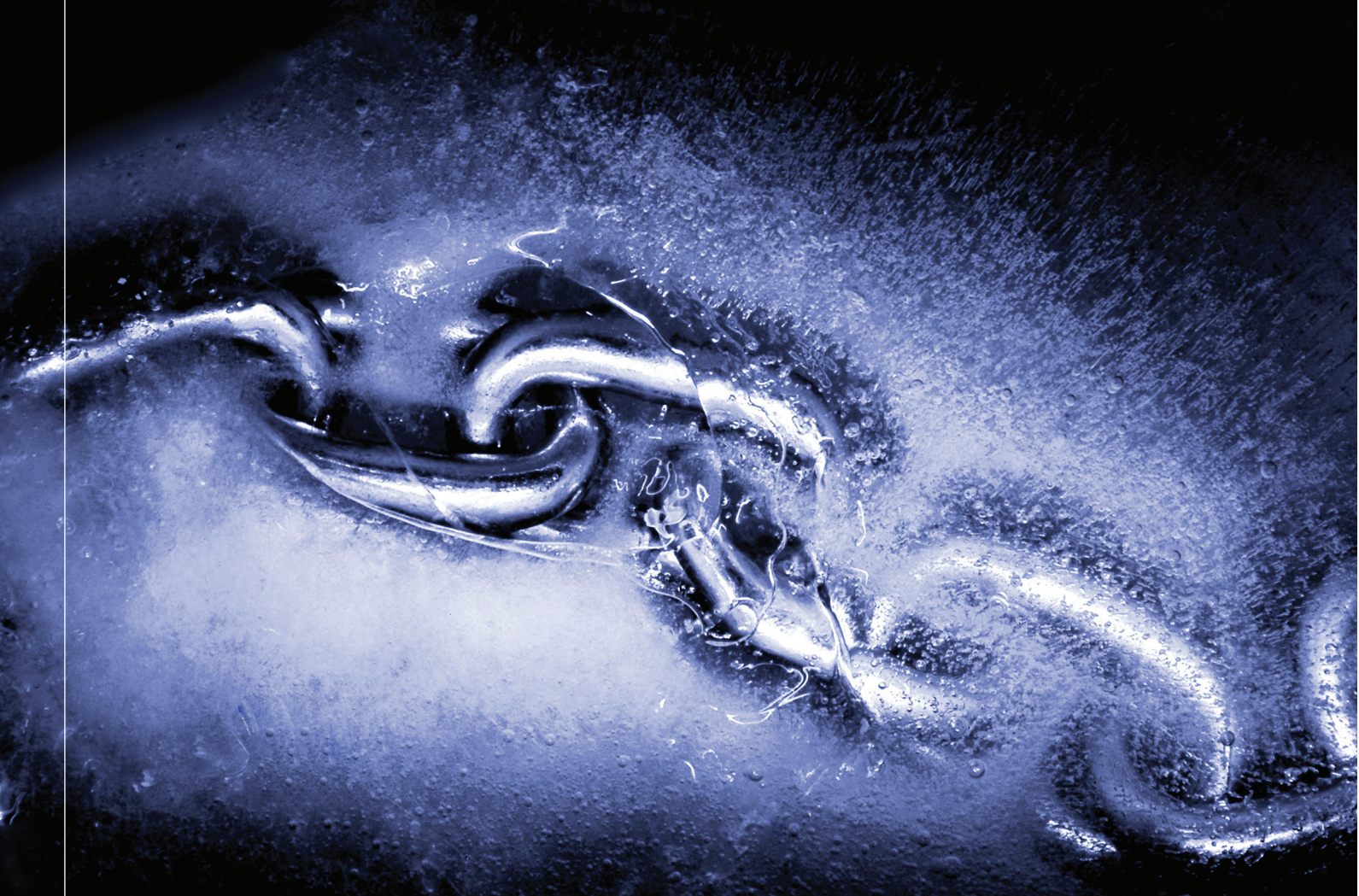

Pharmaceuticals are particularly difficult to transport, with a number of potential areas of weakness within the supply chain. Greater data sharing between partners can provide opportunities as well as challenges. Michael Shaw investigates how new technologies can strengthen pharmaceutical logistics and allow drugs manufacturers to comply with stringent new regulations.

It is a warm spring day in Biberach an der Riss in Germany, when the latest batch of denosumab is mixed, affixed with a serial number, packaged and carefully loaded onto lorries bound for the UK. Designed to reduce instances of bone fractures in osteoporosis and cancer patients, the drug has to be stored at a temperature of between 2–8°C. To that end, as the vials clink at every bump on the autobahn, the medicine is kept in refrigerated containers throughout transportation.

After it crosses into the UK, the lorry is parked at a distribution centre. Here, the consignment of denosumab will be logged by logistics personnel, the number of cases compared to those having left the

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factory at Biberach an der Riss. When the man in the hard hat with the clipboard is satisfied, the medicines are carefully removed from the back of the lorry and transferred to another refrigerated environment. The logistics personnel work quickly. If the temperature of Denosumab rises higher than 8°C, then the medicine only has a shelf life of approximately 30 days.

After that, the final stage of the medicine's journey begins. The original consignment is now divided into several batches, each to be sent to different hospitals up and down the UK. As before, each box is counted in and out, albeit on a smaller scale, before it departs for its destination. A few days later, a vial of denosumab is removed from a fridge at a doctor's surgery in Essex and injected into a patient's leg. Here it will suppress the osteoplasts present in their tibia, helping to regenerate the bone and protect against further degradation.

Such is the typical distribution path of a biologic medicine and in many ways the ideal one. Its success should be judged, as much did not go wrong, by the speed that the vial of denosumab reached the patient. Firstly, the medicine was handled correctly; no accidents resulted in any smashed vials, and the drug was kept at the correct temperature throughout. Neither of the lorries travelling to and from the distribution centre in the UK was diverted from its route and the consignments stolen for resale on the black market. Lastly, the medical authority presiding over its use could, with complete confidence, trace its journey from the factory with pinpoint accuracy, thanks to the serial number affixed to the drug before it was fully packaged.

That any one of these events is, on its own, unlikely to happen is testament to the commitment to innovation and efficiency among pharmaceutical companies over the past two decades. Now, regulators are seeking to enshrine guaranteeing the efficacy and transparency of pharmaceutical supply chains into law. Both the EU Falsified Medicines Directive and the upcoming US Drug Supply Chain Security Act (DSCSA) are pushing industry players to look at radical new solutions to ensure compliance with this new global regime. Only time will tell as to whether it will succeed.

Reduce opacity

What is driving this trend? One factor is the increasing popularity of biologics like denosumab. According to a recent white paper entitled Global Trends in Clinical Trial Logistics: 2020 Perspective, temperature-sensitive medicines now comprise up to 38% of all pharmaceutical products. Most of these require constant refrigeration in a so-called 'cold chain' of distribution from factory to end user, which in turn has spurred significant investment among pharmaceutical and logistical companies that like to equip its own supply lines with the requisite equipment. The costs, after all, of a spoiled batch of biologics – often expensive to manufacture in the first place – could be significant for both producer and patient.

Another factor lies in the desire among medical authorities in North America and Europe to mitigate the impact of scandals involving stolen or poorly made medicines. The former has been a perennial problem; drugs have been used and abused for millennia, and criminals are only too happy to sustain the latter through theft and counterfeiting. In the EU, the Falsified Medicine Directive – in force since February – mandated the inclusion of anti-tampering devices, a unique identifier and stronger record-keeping to diminish the chances of counterfeit drugs appearing on European pharmacy shelves. Meanwhile in the US, the FDA describes the Drug Supply Chain Security Act mandate as the creation of an "electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States", thereby reducing the number of medicines that keep appearing on the black market.

"Being part of the Responsible Health Initiative will help us leverage digital sustainability intelligence to more effectively select and partner with suppliers who share our values."
Valerie Monk, GSK

The emergence of the internet of things (IoT), however, promises to solve this problem. Until recently, the progress of medicines along the supply chain was achieved largely through inventory reports from logistics personnel on several stages of its journey. By attaching trackers – usually small, inexpensive sensors emitting an RFID or Bluetooth signal – to packaging or affixing them to cold-chain units, pharmaceutical companies can obtain a picture of any consignment's location in real time.

Additionally, the use of IoT can provide key insights on where, when and how medicines are being transported to market. It is here that investments in the right telematics solution can become crucial. Not only should pharmaceutical companies be careful in choosing a system that can pinpoint the locations of medicine consignments at any one time, but consider if it can also map entire distribution routes, enabling them to be altered in an emergency, or if it can reveal if certain aspects of the supply chain are inefficient.

This can prove particularly useful when it comes to monitoring the integrity of existing cold-chain supply routes. According to IATA, up to 20% of all

38%
Temperature-sensitive medicines that comprise all pharmaceuticals.
'Global Trends in Clinical Trial Logistics: 2020 Perspective'

20%

Drugs that are ruined because of failures in refrigeration during transport.

IATA

drugs are ruined because of failures in refrigeration during transport, resulting in significant financial and reputational losses for pharmaceutical companies. By monitoring temperature fluctuations during storage and transport with sensors embedded in cargo of biologics, warehouses and logistics companies can be alerted and any spoilage of the consignment(s) avoided.

To that end, the use of IoT across the logistics sector has increased markedly in recent years. One of the first companies to adopt this methodology claims to have spotted over 4,500 suspicious temperature fluctuations during a six-month trial period. Others are experimenting with placing IoT trackers into product packaging, in addition to spending hundreds of millions to enlarge pharmaceutical distribution networks.

Sharing is caring

By weaving IoT technology through their distribution channels, pharmaceutical companies can increase transparency in their supply chains and potentially use the data generated from its installation to make new efficiencies. However, so far its roll-out is proceeding on an company-by-company basis, meaning that improvements in distribution channels are confined to those industry players willing to act first on investment in the technology.

Indeed, the risk that data on manufacturing and distribution could become siloed has led to calls from across the sector for more collaboration between pharmaceutical companies. It was with this goal in mind that GSK, Takeda and Teva signed up for the Responsible Health Initiative, a new scheme intended to harmonise CSR standards between signatories and boost visibility up and down the pharmaceutical supply chain. "Being part of the Responsible Health Initiative will help us leverage digital sustainability intelligence to more effectively select and partner with suppliers who share our values," said Valerie Monk, GSK's head of ethics and risk programmes, in January 2019.

This is just as well. In recent years, demand for more affordable generic medicines has risen markedly in Europe and North America, drugs that are invariably manufactured in developing economies where regulatory scrutiny of active primary ingredients is harder to maintain. This trend has been matched by a dip in regulatory inspections of overseas assembly lines. According to data obtained by PriceWaterhouseCoopers in 2018, FDA approvals of generic drugs had risen to a record high of 971. Meanwhile, the number of inspections of foreign medicines factories had fallen by 11% compared with the previous year.

The necessity of full traceability in the pharmaceutical supply chain, not only taking in the packaging and transportation of relevant medicines but its very formulation, has been underscored by several recent recall scandals. In July 2018, the US was forced to recall valsartan, a generic used to treat high blood pressure, after a minor change made at one of its manufacturers in China led to the contamination of multiple consignments with the carcinogen nitrosamine. This was followed in the following months by a recall of 22 different drugs containing irbesartan and a batch of hydrochlorothiazide over similar fears.

The sector needs to come up with a solution and fast – the DSCSA, after all, mandates unit-level serialisation from manufacturers by 2023. Precisely how this will happen remains unclear, given current confusion about how manufacturers and distributors should best comply with the new law. According to Perry Fri, executive vice-president of industry relations at the Healthcare Distribution Alliance, the gap between the agency's expectations and the reality of how far serialisation could progress in the sector has become boring.

"I think the FDA has a view of kind of a major end-stage place that is a centralised, cloud-based system into which they, and presumably others, could look to examine the path of a particular medicine through the supply chain," Fri told SupplyChainDive in 2018. "I think where the industry is today and frankly how the law is written, we're looking at a visibility system that requires interoperability."

Even attaining this would be hampered by a traditional reticence among manufacturers about sharing information and ideas. "Most people in the industry would prefer that the data is not sitting outside their four walls," added Fri. Perhaps it is as well they should.

Typical vaccine product travelling through the cold chain.

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Esteemed care from start to finish

Transporting pharmaceutical products from origin to destination by air is an exclusive and specialist service that requires high levels of care and attention. **Turkish Cargo** flies to most countries in the world and supports a huge network, including freighter destinations.

Turkish Cargo maintains its ongoing activities in order to realise the best transportation of time and temperature-sensitive pharma and healthcare products, to make the Turkish Airlines network even more integrated via Envirotainer operation requirements by adding QEP accreditation to its most important stations.

Envirotainer's QEP accreditation is proof of the brand reliability within the temperature-controlled freight industry, and the result of hard work and dedication to the customers. Negotiations with Dokasch-TS, an active container supplier, have been concluded successfully and the operation started. The biggest difference on cargo business is its network that enables customers to send pharmaceutical shipments to almost 260 destinations, with new passenger routes consistently opening in Europe and Asia. In order to ensure a high level of reliability and security throughout pharmaceutical shipments, QEP accreditation provides the improvement of ramp-handling processes.

The only way is up

Turkish Cargo has increased the number of QEP-accredited stations to 40 for handling pharmaceutical products; moreover, last in/first out procedure, prioritised loading and unloading, a total of 90 minutes on tarmac for transit shipments, quick ramp transfer and thermal dolly are implemented to minimise the ambient exposure in the pharmaceutical-handling process.

Also, specific SLAs/SOPs are signed with esteemed global solution partners and valuable forwarding agencies for risk mitigation and lane assessment. SOPs cover handling, storage and transportation processes of pharma shipments. Turkish Cargo was awarded IATA's Pharmaceutical and Healthcare Products Transportation certificate 'Center of Excellence for Independent Validators' (CEIV) at its Istanbul Hub, in August 2016.

The company successfully maintains the recertification process that will be performed by IATA every three years. The process of CEIV Pharma-certification for a new airport has already begun.

All in regulation

The company regularly monitors sector requirements in order to transport according to Operational Quality and Pharma GDP standards, completes the deficiencies and continues to realise activities in this direction. In this respect, the company is a member of Pharma. Aero, which aims to achieve excellence in reliable end-to-end air transportation of pharmaceutical products. CEIV Pharma certificate is accepted as the standard by the Pharma.Aero organisation.

Turkish Cargo employs the best equipment to ensure that pharmaceuticals maintain temperature.

"Turkish Cargo has increased the number of QEP-accredited stations to 40 for handling pharmaceutical products."

In order to keep up with the times, some investments should be made continuously in pharma air cargo. The investments must first be made into the facilities, training, and certification required to transport pharmaceuticals safely and securely. Recent cold-chain technology developments provide ensuring temperature condition that are maintain within acceptable limits during transport.

In order to keep up with the times, some investments should be made continuously in pharma air cargo. The investments must first be made into the facilities, training, and certification required to transport pharmaceuticals safely and securely.

Using the right cold-chain equipment is important to reassure pharmaceutical products maintain optimum temperature. Cold-chain equipment can be especially used for healthcare products. In this way, Turkish Cargo builds a bigger and more special dedicated pharma facility at Istanbul Airport. ●

For further information

www.turkishcargo.com

A practical guide

4Advice offers audits, consultancy, in-house support, project management, training and many other services to pharmaceutical companies and suppliers across the globe. Business development director Geert Verniers explains how expertise can ensure logistics companies are agile enough to stay ahead.

The esteemed 4Advice is a young and dynamic consultancy company, founded in September 2015, specialising in international regulations on temperature-controlled pharmaceutical logistics. With EU good distribution practice (GDP) guidelines, WHO GDP chapters and IATA temperature-controlled regulations (TCR) for companies to take into account while operating in this rapidly changing space, its expertise is becoming more relevant and important by the day.

Medicines are meant to save lives, but the quality and effectiveness can only be guaranteed if they are transported under the most optimal circumstances. The company's mission is to bring added value to the pharmaceutical industry and its global and local temperature-controlled supply chain stakeholders. This means assuring the integrity and quality of human medicines throughout their long and complex journeys via sea, air and land towards their all-important final destinations – the patients.

Lead the way

When the EU GDP guidelines became a mandatory standard in 2013, the entire cold supply chain changed. To become or remain trustworthy partners for the pharma industry, many logistics service providers had to rapidly reorganise and adapt while investing in infrastructure and equipment.

Since then, logistics companies have been on the back foot. The main challenge is to implement and maintain compliance with these many requirements across daily operations. Even respected international logistics service providers still struggle with a lack of expertise, know-how and competence to meet the new risk-based approach standards. With its many different stakeholders and complex cold supply chain, the air-freight industry, for one, faces considerable challenges.

In 2014, Brussels Airport took the initiative, gathering a task force in order to implement standards based upon feedback from pharmaceutical companies in the surrounding area. Using a checklist to sort the EU GDP guidelines, the airport successfully implemented its standards among its ground handlers.

The scheme received such positive feedback from local pharmaceutical shippers that the airport authority contacted the IATA to move the programme further. In 2015, the IATA Centre of Excellence for Independent Validators (CEIV) was born. One of Brussels' original task force, Bert Elsen, became the IATA's first independent validator. Elsen is 4Advice's co-founder. Today, the company he helped start is

4Advice offers a range of support and consultancy to all facets of the industry. This polymathic approach serves pharmaceutical companies worldwide.

a strong and reliable partner of IATA. The ultimate goal is to guarantee that pharmaceutical products remain safe and uncontaminated during their long journey from manufacturer to consumer; its three independent validators perform assessments and validation audits all over the world, and each of its employees is in possession of a GDP training certificate.

As a reliable partner of many local and global logistics service providers, 4Advice has many loyal customers in Belgium, France, the Netherlands and Germany, as well as in Canada and the US. All of these partnerships are based upon clients' written agreements to one vital request – the company needs the support of senior management before it starts a project.

The mandatory GDP/CEIV requirements can only be implemented through the entire temperature-controlled operation if decision-makers in management are willing to support and authorise the hard decisions that have to be made. 4Advice cares about the need to improve and maintain the quality and integrity of healthcare products even during the operation, and this cannot be done in half steps.

Travel beyond

The company's goal is to bring solutions, foster continuous improvements and install results-driven best practices that help its customers become experts for themselves. 4Advice makes sure its clients are capable of performing in-house support regarding GDP and CEIV-compliant warehouse projects, operation (re)design, audit programmes, risk and change management processes, lane validations, training and temperature mappings.

Indeed, one of the major challenges on the road to GDP or CEIV compliance are temperature mappings, which are mandatory technical documented studies confirming if the monitoring system and cool devices used in a temperature-controlled room, unit or truck are fit for healthcare products during extreme seasonal weather conditions. 4Advice has carried out many temperature mappings in winters and summers all over the world. It guarantees its customers that its mapping reports are valid and will stand up to each audit or check done by customers or regulators.

Bringing such added value ensures 4Advice satisfied customers who fully trust its services over the long term.

The company is proud that Amerijet, a US freighter, which it supported in becoming CEIV-certified in 2016, recently signed a contract for its online GDP training platform for its blue and white-collar staff in both Spanish and English.

"4Advice is becoming a more recognised and appreciated stakeholder in the pharmaceutical industry, where it is asked to bring expertise and added value."

4Advice is becoming a more recognised and appreciated stakeholder in the pharmaceutical industry, where it is asked to bring expertise and added value to international events, workshops and concrete international projects.

Last year, the company successfully launched its own 'drive.pharma' event in Brussels, gathering pharma shippers, freight forwarders and ground handlers to discuss the future role of transport companies in the challenging pharmaceutical cold supply chain.

In collaboration with its potential clients, 4Advice can ensure that the quality and integrity of medicines will not be affected during transport. ●

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On closer inspection

While there is widespread knowledge of the growth of the illicit drugs trade, pharmaceutical experts say serialisation compliance is only part of the solution. Patrick Kingsland speaks to **Guido Holzem**, senior intelligence manager global GxP & eCompliance QA at Grünenthal; **Pasi Kemppainen**, a management adviser at Santen Pharmaceutical; and **Géraldine Lissalde-Bonnet**, director of public policy at GS1, about how best to protect pharmaceutical companies and patients.

In previous years, the falsified batch of Avastin – a blockbuster cancer drug made by Genentech – would have likely gone undetected. But when a Dutch wholesaler scanned a box full of the drug back in June 2019, an alert system helped sniff out the fake product before it ended up in a patient's unsuspecting hands.

The incident was significant and this is not just because it protected lives: it marked the first time a batch of falsified medicines was intercepted under the EU's flagship anti-counterfeiting regulation – the Falsified Medicines Directive (FMD).

The system – one of a number of similar regulations being rolled out around the world –

Egorov Artem/Shutterstock.com

is designed to put a stop to the global counterfeiting scourge that the World Health Organization (WHO) says costs the lives of hundreds of thousands of people every year, mostly in the developing world.

FMD – which came into force last February – requires that every pack of prescription medicine, sold within a EU member state, has two new safety features: an anti-tampering device and a unique identifier that is readable to both humans and machines, and can be checked at the point of dispense and sale before the medicine reaches the patient.

But while serialisation regulations like FMD have shown some initial success – the batch of falsified Avastin drugs a clear case in point – pharmaceutical experts involved in implementing the regulation say it is not enough to fully stamp out the illicit trade.

Step it up

More must be done, the experts say, to ensure different stakeholders and not just drug manufacturers are responsible for getting bad medicine out of the supply chain, while patients at the end of the line must also be empowered to verify the drugs they ultimately use.

"Serialisation is just the first step," says Guido Holzem, senior intelligence manager global GxP & eCompliance QA at Grünenthal, a German pharmaceutical company.

Efforts to introduce serialisation have been a long time in the making. The FMD directive was first adopted by the European Council and European Parliament in 2011, while the US Drug Supply Chain Security Act (DSCSA) passed in 2013 with a 10 year road map for companies across the pharmaceutical supply chain. Russia, China and South Korea are among other countries also introducing regulations.

Though still in the early stages, the new rules have had both "expected and unexpected benefits," according to Pasi Kemppainen, a management adviser at Santen Pharmaceutical, covering global serialisation and traceability.

The expected benefits, he says, are the level of regulatory compliance and the increase in patient safety. The unexpected benefits include, "better transparency, especially with CMO and CPO operations with regard to packaging operations, quality and shipments", as well as "much better end-to-end supply chain visibility with 3PLs (third-party logistics)".

But challenges still remain. In July, the European Medicines Verification Organisation (EMVO) – the body responsible for running FMD's verification system – said roughly 40% of manufacturers and 25% of supply chain actors were yet to connect to the system. The body said non-compliance should be targeted by national regulators.

"Both the EMVO and National Medicines Verification Organisations stand ready to supply all necessary and available information to National Competent Authorities," EMVO said in a statement.

"The pharmaceutical industry is projected to invest a substantial amount of money and time in the coming years to develop serialisation capabilities to ensure regulatory compliance and to improve patient safety."

Géraldine Lissalde-Bonnet

The compliance process has certainly been cumbersome. Pharmaceutical companies must select the right software and hardware, and then integrate serialisation requirements across their product lines. Packaging has to be totally redesigned, as do the cartons carrying drugs. A number of small to mid-size manufacturers have struggled to comply.

"Initially, benefits of these initiatives, such as the FMD and DSCSA may take a few years before effectively impacting the market," says Géraldine Lissalde-Bonnet, director of public policy at GS1. "As more and more requirements from different countries are being adopted/implemented, and as these are globally aligned, the momentum means that time frames for positive effects on the supply chain will be reduced."

Not alone

While serialisation is considered a major achievement by the pharmaceutical industry, many accept that it is only part of the solution, and cannot solve the problems of counterfeiting and diversion alone.

"Serialisation and traceability significantly increase the bar for supplying counterfeits to the legal pharmaceutical supply chain but there are still uncontrolled sources for counterfeits, especially on the internet," says Kemppainen.

Experts say regulations needs to be combined with other measures, including rigorous enforcement and surveillance by regulators and other authorities, as well as stiff penalties for those that break the rules.

With the pharmaceutical supply chain so large, drug manufacturers cannot be the only ones that follow these rules. Instead, serialisation must be coupled with the exchange of data between supply chain partners as products move through global supply chains.

"Pharmaceutical manufacturers are not the only ones that need to be involved here," says Holzem. "Wholesalers need to understand that they too must follow the FMD rules and all other internationally recognised regulations. It is a combination of all stakeholders working to ensure the supply chain

40%
+25%

As of July 2019, roughly 40% of manufacturers and 25% of supply chain actors are yet to connect to the FMD's verification system.

EMVO

Next-generation anti-counterfeiting

New technologies under development promise the enhanced anti-counterfeiting protections and higher risk/reward payoff that executives say they want. These systems are harder to crack, so they do not require frequent, costly overhauls. They also fill a critical gap by enabling companies to embed identifiers below secondary packaging. If regulatory obstacles can be removed, direct labelling of pills will be possible in some cases.

Moreover, advanced anti-counterfeiting systems go beyond thwarting fake drugs to create value in other ways. The same capabilities that enhance detection of counterfeits also drive supply chain efficiencies. For example, new tracking technologies that follow high-value products through production and distribution — within applicable legal bounds — gather information that can be used to reduce costs in many areas:

- Recalls become less expensive and more efficient when the manufacturer knows exactly where to find all of the affected products.
- The availability of better insights into the amount, timing and location of demand for various drugs makes it possible for manufacturers to predict sales more accurately, manage production more efficiently, and avoid product shortages. Inventory costs decline by as much as 15%, freeing capital for other uses.
- The ability to effectively 'lock' a supply chain for extremely costly products or controlled substances can help reduce expenditures for the special security measures these products currently require. The new technologies can also yield opportunities on the revenue side, particularly by making it possible for manufacturers to generate more sales through digital channels, as improving security boosts customers' confidence in online pharmacies. Data flowing from tracking technologies can also enable a first-to-market manufacturer to differentiate itself in the marketplace, by offering customers valuable data they can't get from suppliers as long as most of the industry is still using older anti-counterfeiting systems. Product codes can include much more than a unique serial number. They can also provide information on a drug's chemical make-up, side effects and other characteristics important to a doctor or pharmacist.

Source: Strategy and PricewaterhouseCooper

is protected and that patients have products that are compliant.

"Activities by law enforcement authorities, such as Interpol's Pangea project, remain important to fight the illicit trade. Patients should be aware of the risks associated with buying medicines from unregulated websites."

Beyond serialisation, many argue that patients must be empowered to check drug products themselves. This would require raising awareness of counterfeiting among end users and then providing them with access to the product information.

"You can't underestimate the importance of patient awareness and education," says Kemppainen. "The last line of defence is the patients themselves and the more aware they are of the risks with buying drugs outside of the legal supply chain, the fewer risks they should be taking with their own health."

GS1 says it has developed a global standard for the purpose of empowering end users. Known as the GS1 Digital Link standard, it gives manufacturers, distributors, hospitals and patients a global standard on which they can base the functioning of tools, such as apps, used to access digital information about certain pharmaceuticals. This standard leverages the existing serialised barcodes and does not require an additional barcode symbol to be applied to the pack, which is key for patient safety.

But introducing systems like this on a wider scale would take time, Holzem cautions. Setting up a patient verification tool that takes too long or has technological problems could "jeopardise trust in the system", he says.

"If this happens it must be discussed and developed properly to ensure patients receive the right information and have confidence that the products in their hands are the right ones."

Not just an issue

The pharmaceutical experts say drug manufacturers should also see serialisation not only as a compliance issue but as a business opportunity. At Grünenthal, Holzem says the company has used the compliance process to reflect on a variety of systems and product flows with a view to optimising general productivity.

In addition to protecting patient lives, Kemppainen says serialisation and traceability initiatives offer a platform for improving supply chain integrity, transparency, operations and "ecosystem collaboration".

Having invested huge sums of money building a pan-EU verification system, now is the time, he says, for companies to start using the data to improve the way they operate internally and conduct business.

"The pharmaceutical industry is projected to invest a substantial amount of money and time in the coming years to develop serialisation capabilities to ensure regulatory compliance and to improve patient safety," says Lissalde-Bonnet.

"While the immediate benefits around ensuring product integrity and eliminating counterfeiting are immense, there are compelling business scenarios in which serialisation can be used to develop new processes and capabilities or supplement existing ones for tangible operational gains.

"Many organisations are undertaking their implementations of serialisation and traceability from a strategic perspective in order to achieve those benefits."

At the moment, the priority for most companies will be smoothing out any teething problems, keeping eyes on future implementation deadlines while also navigating the various other countries that are introducing new regulations.

Over the coming years, Holzem says, serialisation compliance is likely to evolve significantly, "depending on what technological solutions will be available". But while it might seem like a headache, the noble goal of serialisation should not be forgotten, he adds.

"Counterfeit products have already been prevented from penetrating the market [since FMD] so we should keep in mind the high goal here: increasing patients' safety and preventing them from being harmed by falsified products," Holzem concludes.

Outsourcing

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Piece by piece

For over 20 years, contract manufacturing organisations (CMOs) have played an increasingly important role in the pharmaceutical industry. The need to lower the time to market, improve process efficiency and reduce costs are all key factors that have resulted in building on this trend, and will continue to do so for the foreseeable future. Emma Green discusses the key considerations when choosing and working with a CMO.

The use of CMOs provides a number of benefits for pharma companies: gaining access to new technology, adding manufacturing capacity, mitigating risk and opening avenues for entering emerging markets. A 2018 survey by BCG revealed that four out of five executives responsible for selecting outside providers of manufacturing and supply services would like to establish strategic partnerships with CMOs. However, choosing and maintaining these relationships can be challenging. The same survey found that only a quarter of the executives felt that the deals struck had been successful relationships.

Partner up

There are ways to improve the chances of a successful collaboration with CMOs. Carefully thinking about which CMO is going to be best suited for a particular situation is key. Companies must also be clear on what they want, create a playbook to use as a template to structure a deal, conduct thorough financial evaluations and identify contingencies to deal with potential problems that may arise. These help to create and maintain a strong relationship that works for both parties.

Successful partnerships can last for decades. When GlaxoSmithKline (GSK) expanded its respiratory franchise in the 1990s to sell more-sophisticated delivery devices, it partnered with a CMO to deliver Diskus, a dry-powder asthma inhaler that represented a significant improvement over existing devices. By 2010, 500 million of the devices had been manufactured and today the CMO still supports GSK with

the supply of product and ongoing quality improvement activities.

It is not just the greater use of CMOs that is different in the industry today, compared with a couple of decades ago. Previously, external supply functions were virtually non-existent. Instead using CMOs on a decentralised, transactional basis was the norm. Since then, pharma companies have created global external supply organisations in order to streamline the management of CMOs, and other manufacturing materials and services suppliers. As these organisations have developed, executives who run them have come to appreciate the value of making the relationship with CMOs more effective.

This operational shift has occurred in parallel with the change in pharma portfolios from high-volume small molecules to biologics and specialised, often low-volume small molecules, which many companies do not have the capacity to manufacture themselves. CMOs have therefore been increasingly relied upon to provide the required capacity and expertise. Additionally, emerging economies are becoming more demanding in making local manufacturing a prerequisite to granting formulary access or reimbursement. That has resulted in pharma companies seeking out local partnerships as they are considered a more practical, less expensive alternative to building a facility.

Partnering with a CMO allows a pharma company to gain access to new manufacturing technology in a way that is cheaper, easier and faster than building it in-house, as well as being less risky than building it internally before a product has been approved. Products in the pipeline can be crucial to the future of an organisation, so collaborating with a strategic partner, rather than with a traditional supplier, is often the wiser choice.

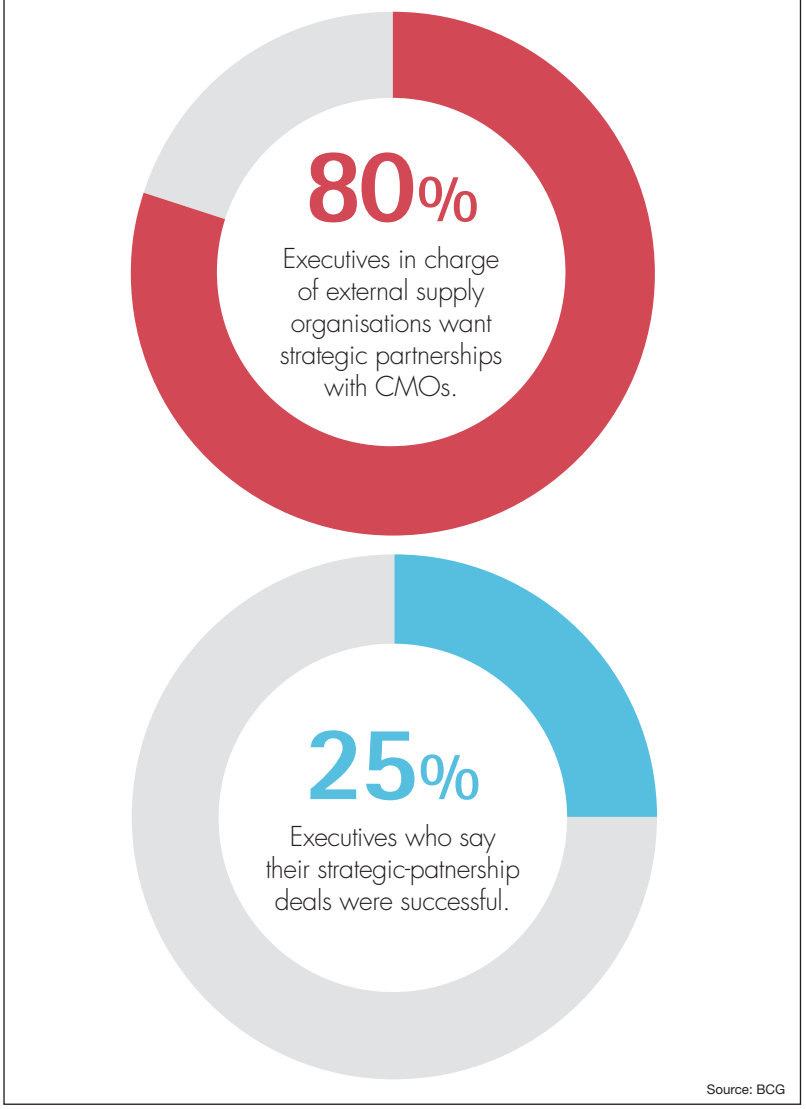
A strategic partnership may be particularly beneficial for a company that is shifting its portfolio from small molecules to large molecules or that is using new or relatively rare technologies. When Seattle Genetics received accelerated approval of the ADC brentuximab vedotin, the company partnered with a CMO to manufacture the antibody and with another CMO to manufacture the cytotoxic drug. These organisations can also provide access to advanced delivery devices such as dermal patches, inhalers and continuous-release mechanisms. Teva Pharmaceutical, for example, used a CMO to make autoinjectors.

CMOs can also help a company shifting its portfolio away from a product that represents a large portion of revenue that is decreasing in value. If the CMO is manufacturing the older product, the company can concentrate internal capacity on newer, higher-value products. For instance, when esomeprazole, Pfizer's prescription heartburn treatment, became an over-the-counter medication, the company lacked the technology required to manufacture the delayed-release, enteric-coated tablets marketed as Nexium. Rather than building capacity internally for an older product, Pfizer entered into an agreement with a CMO that had the necessary manufacturing experience.

The reduced risk provided by the use of CMOs is another advantage. The absence of a contingency plan in the event of a natural disaster, an unexpected surge in demand, or another emergency can create major supply disruption. Building extra manufacturing capacity internally for such events is prohibitively expensive, therefore partnering with a CMO is the next best alternative.

The capital costs of a pharma company are also typically lower than those of a CMO, making it easier to undertake major capital investments. ▶

BCG survey results: pharma companies want strategic partners but efforts have fallen short



Source: BCG

500 million

The number of dry-powder asthma inhaler manufactured by 2010.

GSK

However, commercialising extra capacity if the expected volume does not materialise is challenging. A CMO that co-invests with a pharma company can reduce its exposure by marketing excess capacity to other customers.

The increased localisation requirements of emerging markets is an attempt to foster their own industry and expertise. One way of satisfying such demands is to partner with either privately owned CMOs, or CMOs owned or operated by public agencies or local governments. Pharma companies benefit by achieving fast-track marketing authorisation in the country and are likely better positioned in formularies and to be approved for public-payer reimbursement.

An example of this occurring successfully is Bristol-Myers Squibb's expansion of its business in Brazil by signing a technology transfer agreement with a pharmaceutical laboratory run by the Brazilian Ministry of Health. Bristol-Myers Squibb agreed to transfer manufacturing and distribution of the antiretroviral medication atazanavir, marketed as Reyataz, to the CMO and to train its staff in exchange for approval to sell the drug in the country.

It's complicated

Despite the numerous advantages gained by the use of CMOs, there are a huge number of factors that can derail these strategic partnerships. For example, there may be divergent ideas about how the deal should work, with one party valuing the partnership more than the other or the team in charge lacks the required skills, experience or resources. Discussions about the reasons for using a CMO, what it should cover and how it should be structured financially must begin long before the partnership is in place.

Strategic partnerships are often so complex that the simple contracts used to cover basic manufacturing outsourcing agreements are not sufficient. External supply teams can benefit from an overarching playbook, including contract terms and specifications covering all aspects of the deal. This should clarify the amount of flexibility the company needs in order to make any last-minute changes that might arise within its own operations, while also being mindful that the CMO must have enough wiggle room to meet other client's needs. Similarly, it should detail the requirements of regulators and the pharma company's quality assurance team, while recognising the CMO's need to meet the quality standards of other customers. The playbook should address contingencies.

The use of several financial scenarios can help pharma companies determine the value of potential partnerships versus the cost of keeping manufacturing in-house. Ideally this should entail three types of financial analysis: future volume, direct cost and opportunity cost. To assess future volume, the pharma company should review its long-term plans, estimated future pipeline volume, product demand and the likelihood that new products will be approved by regulators, all of which the CMO must be flexible enough to handle. To evaluate the costs of each type of partnership, the company can analyse minimum-guaranteed-volume requirements, cost per batch, fixed costs with maximum number of batches, costs for additional services and volume discounts. Finally, to analyse the costs and risks of using the CMO, the company can incorporate other value measures, such as the opportunity cost of internal capacity for more valuable products, the risk of single sourcing, or the risk of entering a technological area that the company does not have manufacturing experience.

A major barrier to the long-term success of strategic partnerships is anticipated manufacturing volume that fails to materialise. When volumes are insufficient, the company and the CMO may quickly forget the reasons they collaborated in the first place and revert to negotiating purely on price. This can result in mutual mistrust, which can be magnified when there is an inadequate understanding of what the other has to offer. For the pharma company, that might mean not having enough information on the CMO's services, total capacity, or competing priorities. For the CMO, this might be a lack of realistic estimates of the pharma company's expected volume.

To avoid such events, both companies should be as transparent as possible about volumes, capacity and costs. Once work is under way, they can use KPIs or similar systems to track progress towards the relevant goals and tie each other's performance to clearly defined financial outcomes.

Contracts should also cover situations that could change the nature or value of the relationship for one or both parties. For example, a new owner, a change in corporate management or a shift in pipeline or network strategy. In addition, they should also cover potential future conflicts of interest, such as the CMO's manufacture of competing products or generics, one partner entering the other's business or major changes in volume or CMO capacity.

Although pharma has been slower than other industries to embrace contract manufacturing, the popularity of this approach is continuing to grow at pace. Establishing strategic partnerships with carefully chosen CMOs through well-structured deals can expand capacity and gain access to novel technologies, leading to improved operating efficiencies and increased market share. Furthermore, these relationships can also provide access to emerging and lucrative new markets. Pharma companies that are not exploring such opportunities risk being left behind. ●

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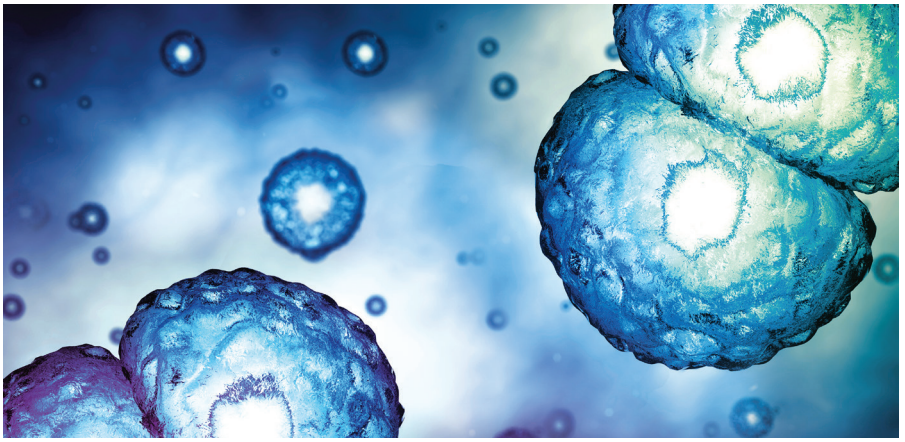
Enhance VLP production

Virus-like particles (VLPs) have become a promising means for vaccination and gene therapy. Currently, vaccines based on VLPs are commercially available for *human papillomavirus*, hepatitis E and B, while others are still undergoing clinical trials. Researchers from the Cell and Bioprocess Engineering Group at the Autonomous University of Barcelona, in association with **Novo Nordisk Pharmatech**, a leading supplier of quats and recombinant insulin, have released a paper exploring the benefits of using insect cell cultures in producing VLPs.

Upon expression, the structural matrix polyprotein 'Gag' from the human immunodeficiency virus (HIV) has shown to accumulate beneath the lipidic membrane. After a sufficient number of the Gag polyprotein is recruited, the assembly process is finished and the virus-like particle (VLP) buds out of the cell. The Gag polyprotein has been demonstrated to accommodate a diversity of protein antigens, underlining their potential as a multivalent vaccine. Several biological systems have been used to produce these nanoparticles, but animal cell lines are the preferred option. Specially, the insect cell/baculovirus expression system (BES) has been proved to work properly for the expression of complex proteins, achieving high protein yields with adequate post-translational modifications.



As a world leader in insulin manufacturing, Novo Nordisk Pharmatech aided in a study that demonstrated the positive effect of r-insulin addition on cell growth and productivity.

"Unlike mammalian cell lines, insect cells provide an easy means for complex protein expression since they can reach high cell densities, do not contain human pathogens and entail less culture requirements."

Unlike mammalian cell lines, insect cells provide an easy means for complex protein expression since they can reach high cell densities, do not contain human pathogens and entail less culture requirements. Among them, the Sf9 insect cell line from *Spodoptera frugiperda* is the most extensively used platform. The *Autographa californica* multiple nucleopolyhedrovirus (AcMNPV) is the typical baculovirus employed for recombinant protein production in this cell line.

Upon infection, the baculovirus arrests the host cell machinery to replicate itself and spread the infection throughout the cell culture. Using standard cloning procedures, the gene of interest is placed after a strong promoter, normally the polyhedrin promoter, to drive the expression of high levels of the recombinant protein of interest. This system consumes an important part of the media nutrients and strategies to increase the production yields of VLPs are then of upmost importance.

Cell-doubling time reduction

Recently, a chemically defined medium for Sf9 cells was developed and there is an opportunity to enhance cell growth and VLP production through specific supplementation. In this study, the effect of recombinant insulin (r-insulin) addition in ExpiSf9 cells using the chemically defined ExpiSF CD medium (Thermo Fisher Scientific) was evaluated. An initial phase of adaptation to different r-insulin concentrations was performed prior to experimentation (1mg/L, 3mg/L and 5mg/L).

The first part of the study focused on the effect of r-insulin addition on cell growth and viability maintenance. A 1.1-fold reduction in cell-doubling time (21±0.5 vs 23.8±2.4 hours) was achieved using 1mg/L r-insulin supplementation. This way, the maximum cell growth was shortened by 24 hours. Also, a 1.2-fold improvement in maximal viable cell concentration was obtained. In the second part, r-insulin was investigated as an enhancer for HIV-1 Gag VLP production using the BES. Again, 1mg/L r-insulin supplementation turned out to be the best condition to increase VLP yield. In these conditions, a 1.2-fold increase in VLP production was attained (5.6×1,010 VLP/mL), all of them with a diameter comprised in the 100–200nm range.

Overall, this work highlights the benefits of 1mg/L r-insulin supplementation in insect cell culture to accelerate cell growth, as well as increasing the maximum VLP titre. ●

For further information

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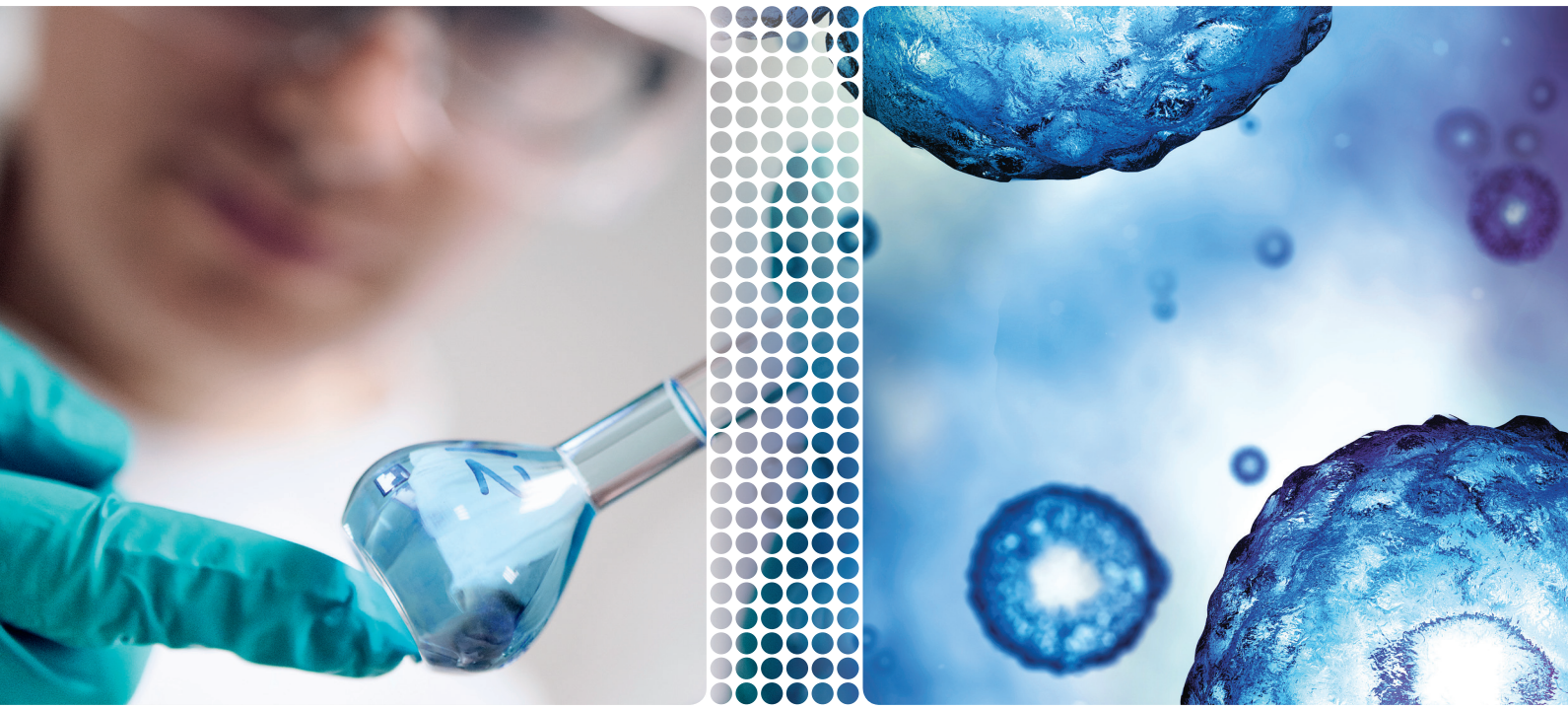


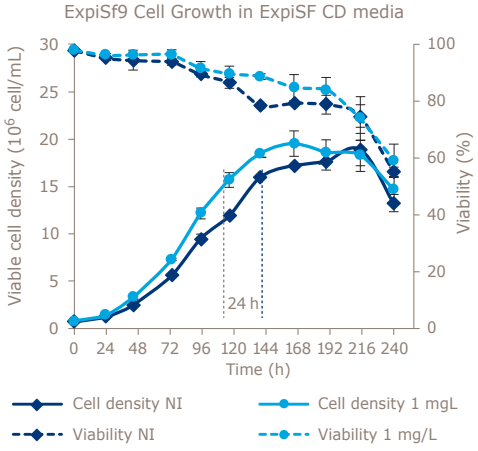
Increase viable Sf9 cell density and Baculovirus-based VLP production by supplementation with recombinant Insulin Human AF

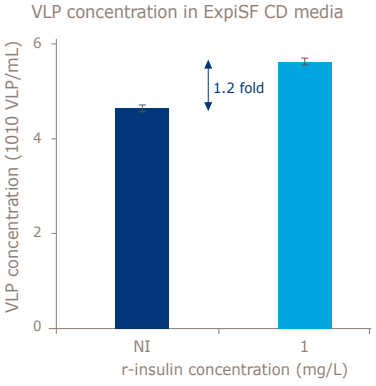
Sf9 insect cells are the most widely used platforms during the manufacturing process of recombinant protein therapeutics when a fast and flexible system is needed. The baculoviral-insect cell system has shown to be a powerful alternative for the production of recombinant proteins in short time frames.

As for the CHO cell-based manufacturing process, increased demand for safety and reliability has moved the standard for Insect cell culture media from Serum to Serum free and further on to chemically defined media.

UAB in collaboration with Novo Nordisk Pharmatech (world's largest supplier of recombinant insulin) has shown a significant increase in viable cell density and baculovirus-dependent VLP production with the addition of animal origin free Insulin into commercially available chemically defined media.

To learn more visit www.novonordiskpharmatech.com





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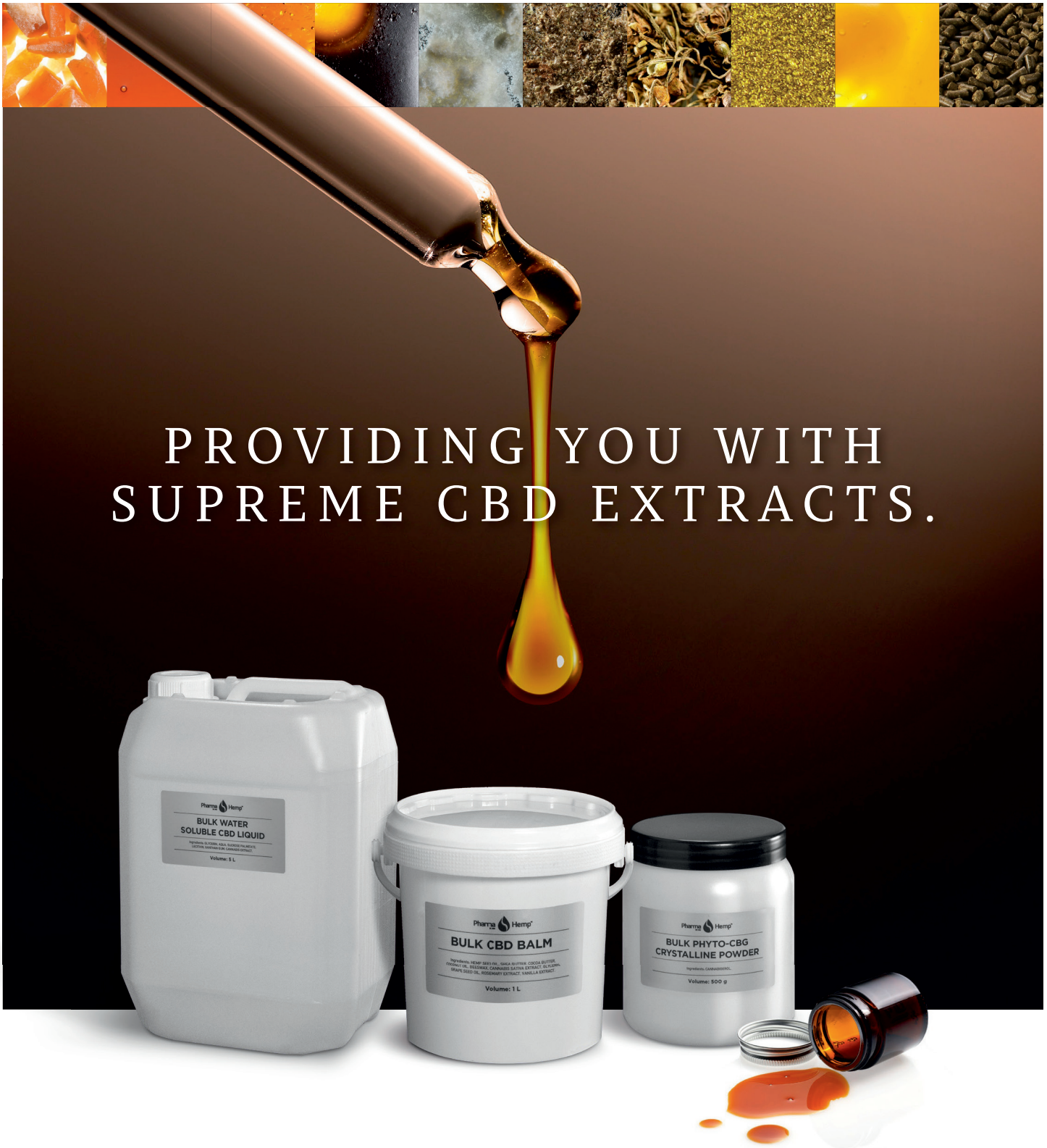

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A move towards a higher bioavailability of phytocannabinoids

Dr Boštjan Jancar, CTO and head of R&D at **PharmaHemp**, explains the new products within phytocannabinoids, the differences between its liquid form and powder form, and how the company tackles enhancing bioavailability.

Over the past few years there has been a significant increase in the number and quantity of cannabis-based products on the market. Numerous providers offer either food supplements or cosmetic products containing various derivatives of the *Cannabis sativa L.* plant. The most popular are different extracts obtained from industrial hemp dissolved in edible oils such as olive, hempseed or MCT oil. Such products are a source of phytocannabinoids, especially cannabidiol (CBD), which has been found to exhibit several health-beneficial properties. Market surveys have revealed that consumers mostly buy these hemp-extract-based products to help them relieve anxiety, cope with pain and fight insomnia.

Oil solutions of lipophilic compounds, such as phytocannabinoids, are known for their low bioavailability, especially through application via oral mucosa. Recently, several providers of hemp-based products have launched what is commonly referred to as a 'water soluble' form of the popular phytocannabinoid CBD. Such a form is usually advertised to considerably increase bioavailability of this phytocannabinoid compared with widespread oil solutions.

'Water soluble' phytocannabinoids

Phytocannabinoids are terpenophenolic compounds that are by chemical nature lipophilic and therefore insoluble in water. The term 'water soluble' CBD is thus misleading and usually refers to oil-in-water emulsions where liphophilic phase (oil solution of CBD) is dispersed in the form of tiny droplets through the continuous phase (water). The stability of such emulsion is achieved by using an appropriate combination of emulsifiers, co-emulsifiers and oils.

New products

PharmaHemp has developed a platform based on different emulsifying agents that enables the formation of stable oil-in-water emulsions of hemp extracts containing a broad spectrum of phytocannabinoids. These emulsions consist of micelles with hydrophobic core and hydrophilic shell, and are as such expected to increase the bioavailability of phytocannabinoids contained in the core of the micelle. Two different forms have been put to market, the liquid form and the powder form. The liquid form is produced by using selected emulsifiers and co-emulsifiers in a glycerine-water system, through utilising high-shear and ultrasonic processes. The powder form is produced by fluidised bed spray coating of emulsions onto different carrier particles. In both cases, contact with water results in the formation of stable oil-in-water micellar emulsion with phytocannabinoids in the hydrophobic part of the micelles.

A new era has begun in the oral availability of CBD.

Clinical study

To substantiate expectation of higher bioavailability, PharmaHemp launched a clinical study in which bioavailability of CBD through oral administration of micellar phytocannabinoid emulsion will be compared with that of oral administration of hemp extract dissolved in hempseed oil.

From previous investigations including animal studies, the oral bioavailability of CBD has been shown to be very low (13–19%). It undergoes extensive first-pass metabolism, and its metabolites are mostly excreted via kidneys. Plasma and brain concentrations are dose-dependent, and bioavailability is increased with various lipid formulations. However, despite the breadth of use of CBD in humans, there is little data on its pharmacokinetics (PK). Analysis and understanding of the PK properties of CBD is critical to its future use as a therapeutic compound in a wide range of clinical settings, particularly regarding dosing regimens and routes of administration. According a the report on PK of cannabidiol in humans, there is a great paucity in data and some discrepancy in the PK of CBD, despite its widespread use in humans. Analysis and understanding of properties such as bioavailability, metabolic and elimination rates are crucial for future therapeutic success, and robust data from a variety of formulations is required. ●

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AJA Pharmaceutical Industries Company

Vision of the future

Despite exporting a small percentage of non-oil products worldwide, Saudi Arabia is looking to diversify its economy, encouraging more localised manufacturing and less reliance on foreign imports. Dr Faisal Bin Dail, deputy general manager of **AJA Pharma** and chairman of National Committee for Pharmaceutical Industries, talks about the company's plans to expand by capitalising on its state-of-the-art production plant in Hail to become a high-quality manufacturing hub for global pharmaceutical markets.

What is the Saudi Vision 2030?

Dr Faisal Bin Dail: Adopted as a blueprint to diversify the economy in the kingdom of Saudi Arabia, Vision 2030 is a detailed plan that touches on many areas within the market: tourism, the development of self-sustainable cities, renewable energy and privatisation. In its desire to harness local technologies the plan signifies a bold new step for the pharmaceutical industry.

How important is Saudi Arabia to international pharmaceuticals?

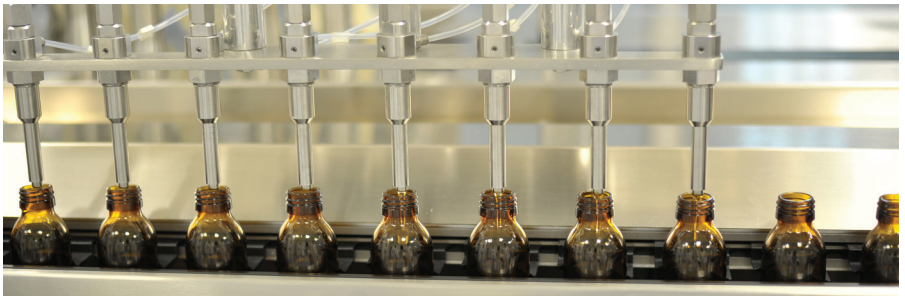
Currently the pharmaceutical market of MENA is small compared with other markets, roughly contributing 3%. However, it is an emerging market, especially with estimates predicting 5–6% growth reaching $60 billion by 2025. Saudi Arabia is the biggest contributor in the region in terms of value.

The Saudi Vision 2030 places more emphasis on private partnerships, providing a growth avenue for global companies to invest and do business in the region, whether that involves pharmaceutical products, technology transfers or healthcare services. Moreover, due to stringent regulatory bodies, companies can be assured that products produced within the region will be of a high standard.

The future holds a lot of promise for pharmaceutical companies hoping to tap into the Saudi market, both from a consumer and sourcing point of view. Saudi Arabia can become a logistics and sourcing hub for the global pharmaceutical markets.

How does AJA Pharma foster collaboration between local and international companies?

AJA Pharma has set up a state-of-the-art manufacturing plant, offering integrated pharmaceutical services to both global companies in Saudi Arabia and to companies that are looking to enter the local market. The company has an in-depth knowledge of regulatory issues, technology transfers, manufacturing, and can also assist with marketing and sales. Our aim is to use our in-depth local knowledge to foster influential long-term partnerships.



AJA Pharma looks to expand its factory production line geographically as well as industrially.

What are the advantages of manufacturing in Saudi Arabia?

Manufacturing here blends high industrial standards with a competitive cost structure. Moreover, due to Vision 2030, locally manufactured products are encouraged by our national regulatory bodies.

Could you outline the upcoming regulations favouring locally manufactured products?

Localisation is favoured to ensure availability of the essential medicines in the country without any disruption. Therefore, while regulators ensure the quality of products, there is a focus by government and private healthcare establishments to purchase more locally manufactured products.

What are the advantages of manufacturing products in Hail?

AJA Pharma chose Hail for its manufacturing plant for logistical reasons. Due to its central location, it connects major cities in Saudi Arabia. It also has a university with a pharmacy college that provides a consistent stream of well-qualified staff members.

What are the technical capabilities of the AJA pharmaceutical plant?

AJA Pharma is a platform for quality and excellence, and the plant is state of the art with high GMP standards. We offer finished formulations as oral solids, semi solids and liquids in non-sterile area, and lyophilised and sterile liquid injections under isolation technology in the sterile area. Our warehouse adheres to the modern supply chain concepts of storage, dispensing and dispatch. The packaging facility is automated with serialisation and aggregation systems.

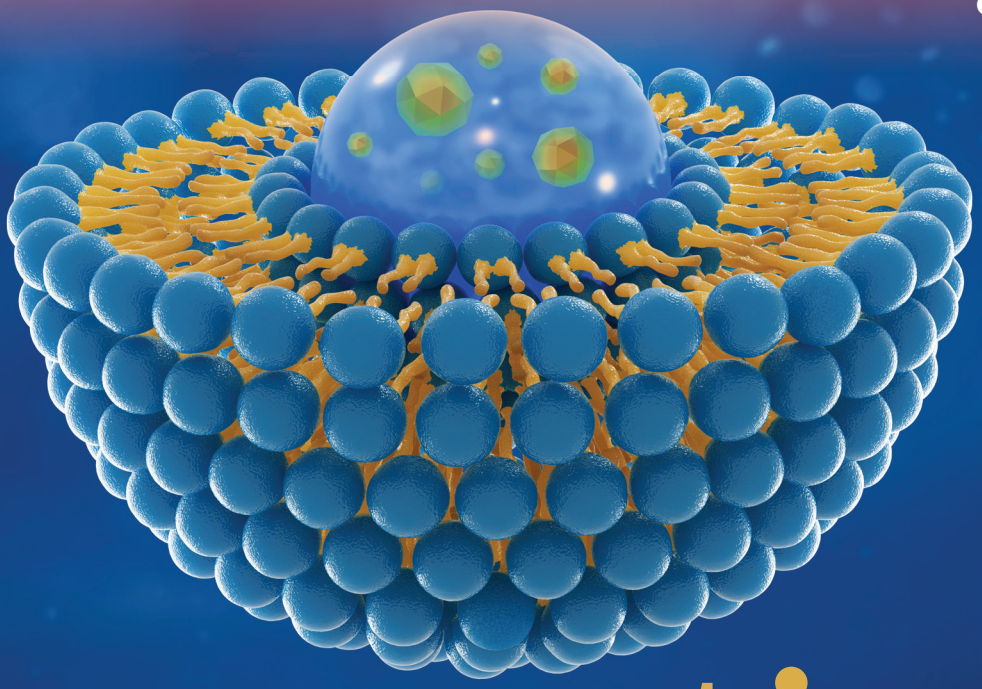
We strive for high-quality operations with controls in place to ensure our methods are safe and reliable. In a short span of time AJA has attracted some well-known global companies to manufacture their products.

How is the company looking to expand in the future?

We are looking to expand geographically, as well as industrially, adding more production lines. The aim is to make our manufacturing facility a hub for safe and reliable pharma products as well as making Saudi Arabia synonymous with high-quality pharma. We also want to expand our offering by adding new dosage forms, new therapies and technologies to cure patients. Ultimately, we want Saudi Arabia to become a key destination for manufacturing finished form products supplied to western markets in both the US and Europe. ●

For further information

businessdevelopment@ajapharma.com



Generation excipients

There are a number of different parenteral-grade excipients used in biopharmaceutical formulations. Deciding between them can be challenging, particularly in light of today's stringent regulatory requirements. Abi Millar speaks to **Rajsekhar Paul**, fellow at Novartis, focusing on late-phase pharmaceutical development in biologics, about moving beyond pharmacopeia to next-generation parenteral excipients.

The global excipients market is growing fast. According to research by Markets and Markets, it will reach $9.7 billion in 2025, up from $6.9 billion in 2019. This growth, which mirrors the growth of the pharmaceuticals market in general, is spurred by advancements in functional excipients, rising adoption of orphan drugs and increased uptake of biopharmaceuticals.

While the market is still dominated by oral formulations, parenterally administered drugs are catching up. Many of the new molecules in the pipeline (especially biologics and targeted oncology drugs) are poorly soluble and difficult to formulate as oral solids. This is fuelling demand for parenteral-grade excipients, a segment that is growing more quickly than the market overall.

In essence, parenteral formulations can include any preparation that will be administered directly into the systemic circulation. According to the market intelligence company Kline, there are three main types of parenteral formulations: liquid solutions, lyophilised (freeze-dried) products and suspensions. Liquid injectable solutions comprise 72% of the market.

In the past, most of these liquid solutions were supplied in single-dose glass or plastic containers, but today the sector is moving towards prefilled pens or syringes. These are generally plastic and disposable, and make injections much easier to administer.

Development challenges

Compared with other administration routes, parenteral formulations pose a unique set of challenges for the drug developer. On one hand, they are more easily absorbed than oral formulations and do not suffer the pitfalls of first-pass metabolism. This

means a parenteral excipient, compared with an oral excipient, may not need to work quite so hard at enhancing bioavailability.

On the other hand, there can be issues associated with drug stability and poor solubility. If the API and excipient are not fully compatible, the API can be degraded and impurities can form. On top of that, while an excipient may work synergistically with the API, there is also a risk of unwanted reactions with the packaging components.

As Rajsekhar Paul, fellow at Novartis explains, there are a few main considerations drug developers need to bear in mind when selecting the right parenteral-grade excipient.

"The main consideration would be that the degradation of the drug product needs to be stopped, or controlled to a certain level, as well as particle formation," he says. "It can definitely be a challenge to make the molecules stable, because aggregation, degradation and association between molecules all play a big role."

As he points out, the excipients in a parenteral formulation need to fulfil several key functions. These include enhancing the solubility of the API, increasing shelf life, and controlling pH and tonicity. Above all, they need to promote stability. Since protein therapeutics (such as monoclonal antibodies) are inherently unstable, excipients are tasked with suppressing protein aggregation and other forms of physical degradation.

Paul says he tests the stability of the formulation by using accelerated stability tests, in which the product is stored at elevated stress conditions.

"I'll do 25°C and 40°C stability chamber studies with 40% and 60% relative humidity, and look at the protein aggregation level," he says. "This can be soluble aggregates, insoluble aggregates or particle matter. I think the main aim is to have a purer compound, quality-wise, so depending on the molecule we need to feel like the final formulation shows the least aggregates."

While there is a huge range of excipients on the market, such as sugars, salts, lipids and polymers, not all of these are suitable for parenteral formulations. For instance, given the high-sterility requirements, the excipient must be able to withstand terminal sterilisation or aseptic processing. Parenteral preparations need to be pyrogen-free and (in the case of a liquid solution) remain soluble throughout the entire shelf life of the product.

Depending on the formulation, some potential additives may include antimicrobials, bulking agents, chelating agents, solubilising agents, tonicity-adjusting agents, antimicrobials and protectants. These will be added to a vehicle such as water, oil or a water-miscible solvent.

Many parenteral formulations also include a buffer system that protects the product against degradation and controls the pH. Buffers commonly used for the purpose include citrates, acetates and phosphates, along with certain amino acids.

"The buffer system is always targeted to the physiological pH, but since different buffers can also exert an effect on the pH, the concentration of the buffer is very important," says Paul. "Sometimes the buffer concentration plays a very big role in the pH shift, and other times it actually hinders the pH shift that is intended."

72%

Liquid injectable solutions comprise a large portion of the market.

Kline

"More and more people are talking about the limitations of injectables with regard to injection course and increased viscosity."

He remarks that no one excipient is suitable across the board. While some common parenteral-grade excipients include PEF-polysorbates and sugars like sucrose and trehalose, each of these has its own potential pitfalls.

"The problem with trehalose is that it crystallises in many different conditions," he says. "It can crystallise upon storage, and in the case of lyophilised products it can also crystallise during the lyophilisation. So in these cases I think trehalose is not suitable. Sucrose is also very commonly used

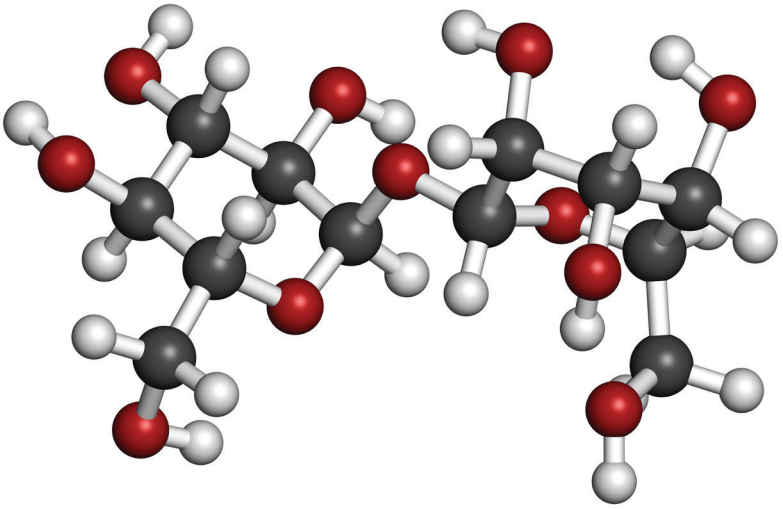
"The organic chemicals segment is to dominate the pharmaceutical excipients market in 2019."
On the basis of product, the pharmaceutical excipients market is segmented into three major categories— organic chemicals, inorganic chemicals, and other chemicals. In 2018, the organic chemicals segment accounted for the largest share of the pharmaceutical excipients market. The large share of this segment can be attributed to the use of these chemicals in the majority of pharmaceutical formulations available in the pharmaceutical market.

"By functionality, the fillers and diluents segment is expected to account for the largest share of the pharmaceutical excipients market in 2019."
On the basis of functionality, pharmaceutical excipients are categorised into fillers and diluents, binders, suspending and viscosity agents, flavouring agents and sweeteners, coating agents, colorants, disintegrants, lubricants and glidants, preservatives, emulsifying agents and other functionalities. The fillers and diluents segment accounted for the largest share of the pharmaceutical excipients market in 2018. The large share of this segment is attributed to the increased use of fillers and diluents in the development and production of solid oral drugs, and the advantages they offer to manufacturers and patients.

"By formulation, the oral formulations segment is estimated to account for the largest share of this market in 2019; however, the topical formulations segment is estimated to be the fastest-growing segment."
Based on formulation, the pharmaceutical excipients market is segmented into oral, topical, parenteral, and other formulations. In 2018, oral formulations accounted for a major share of the pharmaceutical excipients market, mainly because oral formulations are the most common route of drug delivery.

The market for topical formulations is expected to witness the highest growth during the forecast period. Growth in this segment is majorly due to better assimilation of topical excipients with liquid APIs and increased patient compliance due to sensorial effects.

Source: MarketsandMarkets



Above: Atoms of a Trehalose sugar molecule, a common parenteral-grade excipient.

Opening page: 3D rendering of a liposome structure cell.

commercially, and I have seen galactose and glucose used in other cases. Polysorbate is very widely used for parenteral drug administration for injectables, but you have to take care with how it degrades with regard to oxidation."

Given these challenges, some new molecules may require excipients to be used in novel ways, or they may require new excipients altogether. Excipient manufacturers have various ways of achieving this end: they might modify an existing excipient, or create an entirely new chemical entity.

Slow innovation

Unfortunately, innovation in this field is progressing less quickly than one might expect, thanks in no small part to the associated legislative requirements. As novel excipients are regarded as new substances, the regulatory pathways are longer and more complicated (not to mention more expensive) than they would be in the case of established excipients. It does not help that excipients can only be approved as part of a formulation, rather than as products in their own right. This means, if the final product failed, the new excipients within would also fail to gain approval.

The International Pharmaceutical Excipients Council (IPEC) works hard to develop and harmonise standards in this field, as well as promoting the development of new excipients and creating guidance about best practice.

"You need to have a compliant excipient, so you need to have things that don't exert any kinds of side effects as well as guaranteeing stability for the shelf life of the product," says Paul. "There should not be any new excipient that is not pharmacopoeia-compliant, so there is very stringent regulation there. There should be toxicological data that shows that the excipient is safe and efficacious and there are also dose limits guiding how much of the excipient you can use."

It is easy to see, then, why a drug developer might prefer to play it safe and stick with what they know. That said, it seems clear that some of tomorrow's medicines will require next-generation excipients. Particularly as drug delivery systems change (think nanotechnology-enabled drug delivery systems and liposomal drug delivery systems) the pharmaceutical industry will be on the lookout for novel excipients that are multifunctional, high-tech and safe to use.

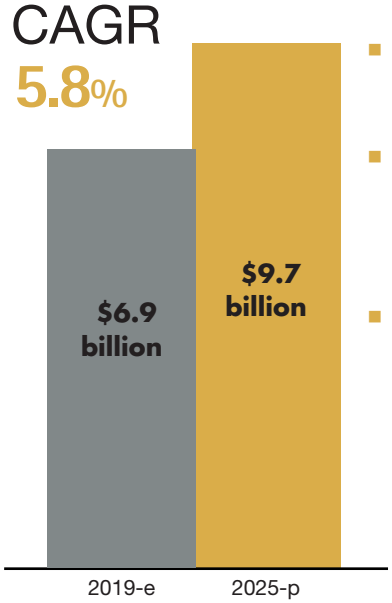
Failing that, they will be looking to develop new and creative formulations. As Paul points out, we are currently seeing a research trend towards non-ionic excipients, as well as formulation systems that are less viscous than what has gone before.

"More and more people are talking about the limitations of injectables with regard to injection course and increased viscosity," he says. "This means there is a trend to look for viscosity reducing agents; for example, where you have a charged basis that creates a responsive force and a negatively or positively impulsive force."

While Paul works with more traditional excipients, he believes the industry in general could be about to fork out into some interesting new directions.

"We are seeing a shift towards different kinds of formats of the API itself, so these days the monoclonal antibody isn't being considered only as a parenteral product, as it was when I started my career," he says. "So I think the complexity is increasing and the need for novel excipients is definitely there."

Growth of the pharmaceutical excipients market



- The pharmaceutical excipients market is projected to reach $9.7 billion by 2025 from $6.9 billion in 2019, at a CAGR of 5.8% during the forecast period.
- The key factors driving market growth include the growth of the pharmaceuticals market backed by functional excipients, a surge in the generics market, increasing uptake of biopharmaceuticals and the rising adoption of orphan drugs.
- The emergence of multifunctional excipients, shifting focus of pharmaceutical manufacturing to emerging markets and the growing biosimilars industry are expected to offer significant growth opportunities for market players during the forecast period.

Source: MarketsandMarkets

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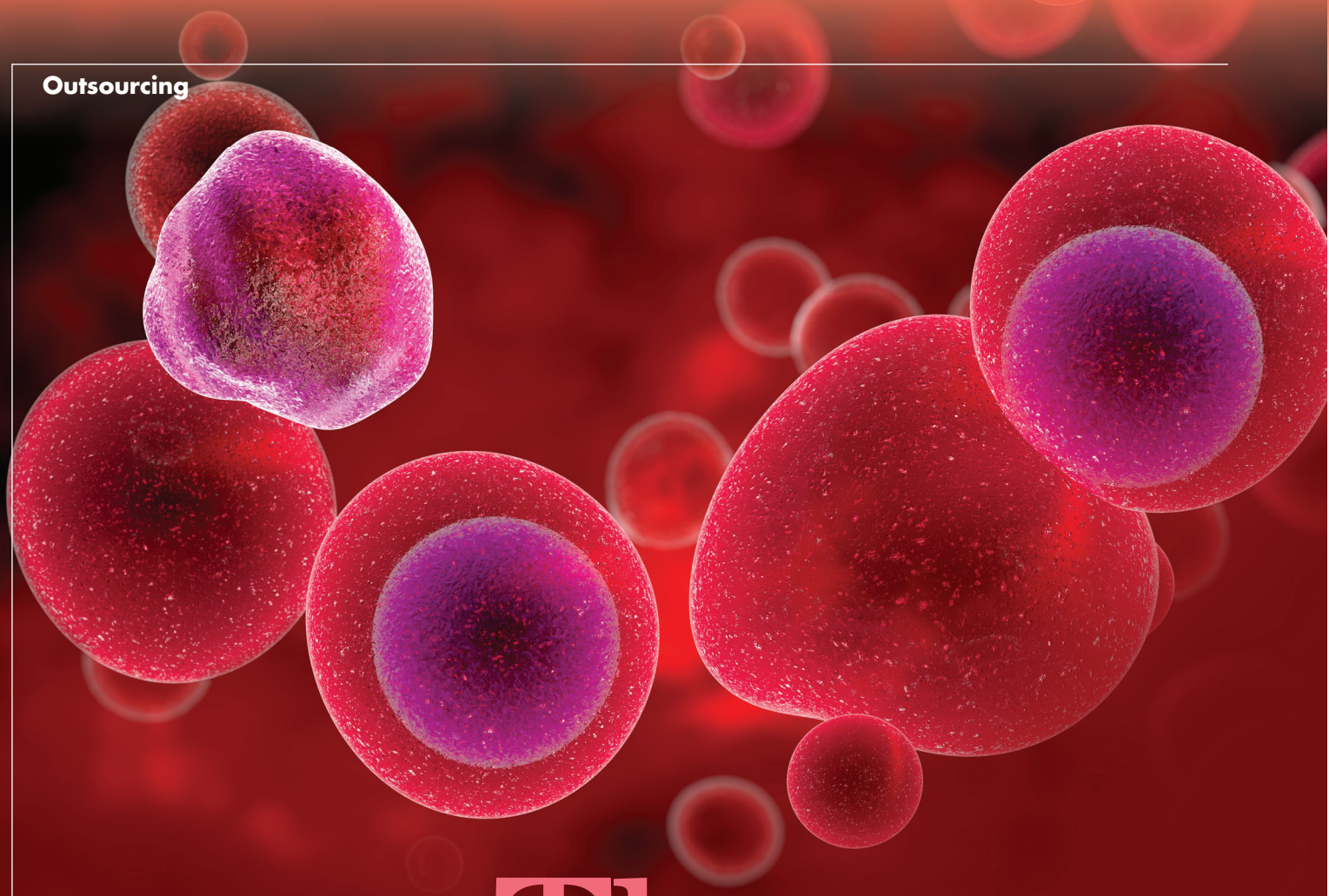


The circle of life

Manufacturing a cell or gene therapy is difficult and costly. Unlike other types of drugs, these living cells demand a sophisticated and circular process that is individuated for each patient. **Minh Hong**, head of commercial development for cell therapies at Lonza, speaks to Louise Thomas about optimal strategies when manufacturing these drugs, including how to choose the right technology.

The field of cell and gene therapy is transforming the way in which patients can be treated. These novel drugs offer drastically improved patient outcomes and, in some cases, can even be curative. The ability to cure diseases is a unique advantage compared with the traditional medications that focus on alleviating symptoms and thus many pharma companies are investing heavily in the field.

There are a wide range of definitions of cell and gene therapies, with some companies even having their own. Minh Hong, head of commercial development for cell therapies at Lonza, explains how the company distinguishes between the different types of therapies.

"Broadly speaking, cell therapies is where the product that we're making is cells themselves and they could be autologous or allogeneic cells," says Hong. "These are used, for example, for tissue repair, cancer vaccines and cellular immunotherapies."

Gene therapies, on the other hand, are "when you start touching the genome of the cell and you try to alter it, either in vivo or ex vivo, using a viral vector or some type of non-viral approach. There are two main types of gene therapies, binary modified gene therapies and non-binary modified gene therapies," says Hong.

Giovanni Cancemi/Shutterstock.com

Keep up

Genetic diseases and cancer are the two key areas of focus for these therapies. With huge potential to be able to treat and even cure these conditions, the industry is keen to establish proof-of-principle for drugs as quickly as possible. A look at the scientific literature around cell and gene therapies demonstrates the rapid pace in which the field is moving. "You have to keep up with the research out there because developments change every day," says Hong. "There is something new happening all the time."

Developing a traditional therapy typically takes between seven and 15 years to get the product into the market. In contrast, cell and gene therapies, from proof-of-concept to commercialisation, can take as little as three to four years.

Despite the speed of developments, it is important to remember that the field is young and still grappling with growing pains. "People used to say it was in its infancy; I think personally now it is in its teenage years," says Hong. "In the explosion and recent growth that we are experiencing, we have tons of pressure and responsibilities to deliver on these therapies."

In order to keep up with the field, regulation is having to adjust its ways of working. "The paradigm and frameworks of how these therapies are being developed is shifting," says Hong. "For example, with fast-track approvals, regulators are really trying to help get these therapies to patients as quickly as possible."

Overcome obstacles

The need for speed is complicated as it raises a number of difficulties, particularly in terms of manufacturing, which the industry is still working to overcome. "We're seeing pioneering technologies, developing novel practices, or paradigm-shifting practices and taking a close look at bioassays and analytics in order to scale-up and meet the demand needs," says Hong. "Although at the moment we are talking about a relatively small patient population, the goal is to bring this to the masses."

300,000ft²

One of the largest dedicated facilities for the manufacture of cell and gene therapies opened in April 2018 in Houston, US.

Lonza

"In the explosion and recent growth that we are experiencing, we have tons of pressure and responsibilities to deliver on these therapies."

Raw materials pose another challenge for cell and gene therapies, which are very costly. "We're seeing an explosion of demand for critical raw materials and very little supply," says Hong. "We are talking anything from staple consumables all

Left: Innovations and investigations into cells continue at a pace.

Below: Lonza's facility for the manufacture of cell and gene therapies.

Lonza

Sci-Fi or reality?

Since the introduction of science fiction, the popular press has toyed with the notion of viral gene delivery and its terrifying implications. One of the more recent popular works on the topic is the 2007 adaptation of Richard Matheson's classic 1954 novel, *I Am Legend*, which details events following the discovery, release and mutation of a genetically re-engineered measles virus that was initially hailed as the cure for cancer. This adapted novel, which has been redone in three instances as a feature film, outlines the seemingly inevitable worldwide destruction that could result from viral gene therapy. With an emotionally stirring history of fictional violence and a debate that provokes both moral and medical issues, it may be surprising that, since 1990, billions of dollars have been spent on hundreds of human viral gene therapy clinical trials. Our society is in the midst of a paradigm shift that began with the discovery of viruses as dangerous infectious agents and will end with the use of viruses to cure disease and regenerate tissues.

On 19 January 1989, the director of the National Institutes of Health (NIH), Dr James Wyngaarden, approved the first clinical protocol to insert a foreign gene into the immune cells of persons with cancer. On 14 September 1990, W French Anderson and his colleagues at the NIH performed the first approved gene therapy procedure on a four-year-old girl born with severe combined immunodeficiency. Despite the viral horror stories written by the popular media, this initial trial was largely a success and the most recent report on this individual in 2004 noted that she is thriving as an 18-year-old teenager in suburban Cleveland. Over the next 10 years, 300 clinical gene therapy trials were performed on about 3,000 individuals. The field was then blackened with the death of an 18-year-old male four days after the introduction of 38 trillion particles of recombinant adenovirus into his liver. Despite this tragedy, we continue to move forward because of the great promise of novel genetic treatments that, when perfected, will likely outshine current methods, such as protein therapy or pharmacotherapeutics, for treatment of many diseases and defects.

Source: *The Journal of Dental Research*

3–4 years

It takes three to four years to develop cell and gene therapies in contrast with traditional therapy's seven to 15.

Lonza

the way through to critical raw materials, such as viral vectors."

In order to address these challenges, in April 2018, Lonza opened one of the world's largest dedicated facilities for the manufacture of these drugs in Houston in the US. The 300,000ft^2 clinical and commercial manufacturing facility manufactures everything; for example, viral vectors through both autologous and allogeneic therapies, which is substantially expanding the company's capacity to develop cell and gene therapies on a large scale.

"We want to be able to launch millions of personalised therapies and be on a par with the manufacturing of standard drugs. That is going to be a huge challenge for sure but I think it is possible with the enabling technologies that are being developed."

Central to tackling the obstacles in the field is being highly strategic, right from the start of the process. "I think a lot of times we're always in a rush to show proof of principle and we think that the processes are good enough," says Hong. "But when we really think about getting these drugs to the market, we find that the earlier you can address the process gaps, you can save months or even years, by not having to backtrack."

Cell and gene therapies, due to being comprised of living cells, also pose logistical issues. "Historically, you can make batches of active pharmaceutical ingredients (API), store them and then ship when needed," says Hong. "For cell and gene therapies, these tend to be fresh products, so if you're trying to serve a patient population 100,000 batches a year, that is a huge amount to be dealing with on a daily basis."

Communication and collaboration are paramount to addressing these difficulties. "We have to basically create an ecosystem that ties all these different aspects together," says Hong. "We can't operate in silos; we have to work with our partners in this industry in the front and the back end. Developing these manufacturing execution systems is super important."

In light of the increasing demand for these therapies, scaling up represents an important challenge to be tackled. "Automation is going to be a key player to ensure commercial viability," says Hong. "Platforms are also important. Lonza, for example, has invested a lot in a device for autologous cell therapies and in the oncology space, we've invested a lot of effort in developing platforms in the 3D area."

With the field moving so quickly, making any future predictions, on a company or industry level, is not an easy feat. "I wish I had a crystal ball," says Hong. "We have had five product launches in the past 18 months to two years or so. It is just amazing to see so many of these concepts go from manufacturing to commercialisation in such a short amount of time."

The holy grail

Lonza has lofty goals for its cell and gene therapies but Hong is confident that these can become a reality. "In order to achieve this, we are going to see a wave of mass customisation; we are going to have to use novel customised technologies to make this happen," says Hong. "We want to be able to launch millions of personalised therapies and be on a par with the manufacturing of standard drugs. That is going to be a huge challenge for sure but I think it is possible with the enabling technologies that are being developed."

The ultimate goal is establishing these drugs as standard treatment, which may not be far away. "I believe cell and gene therapies will reach the masses and become an integral part of medication regimes for multiple conditions," says Hong. "That is the holy grail but I think it is achievable within the next five to 10 years."

The smart money

Smart packaging offers huge value to the whole of the supply chain. There are a number of recent innovations that can help optimise monitoring. Louise Thomas speaks to **Ruud van der Geer**, associate director supply chain management EMEA, MSD, about the opportunities and future directions within the field.

With a number of data-driven, AI-oriented and trending technologies already impacting the pharma industry, smart packaging is one of the latest developments to help optimise the supply chain. Offering benefits to manufacturers, suppliers and patients has huge potential to transform the way that drugs are transported and the information available throughout this process.

Ruud van der Geer, associate director of supply chain management EMEA, MSD, is passionate about packaging. Currently based in the Netherlands, he has been at MSD for 16 years, initially employed as a packaging engineer before working his way up to his current position. Particularly focused on Europe, the middle-east and Africa, his key interest is in the digitalisation of MSD's logistics network, where smart packaging plays a key role.

The three key areas

For Van der Geer, smart packaging can be divided into three different areas. The first of these relates to the operating model used at MSD, which provides multiple benefits. "What you see a lot is single-use systems in the market; we are changing that to reuse, reverse logistics and pay-per-use models," explains

Smart packaging is one of the latest developments to help optimise the supply chain.

Van der Geer. "This is partly for sustainability; avoiding transport packaging ending up as landfill but also so that we can integrate technology into the system."

Connectivity is another key aspect of smart packaging. "We are taking advantage of new insulated packaging materials that can reduce weight and increase quality," says Van der Geer. "Everyone is using USB devices but with the new technologies entering the market, they allow us to be more proactively connected to GPS and cell networks."

A less obvious element of smart packaging is the people involved. "We need to make sure that we have strategic partnerships and strong collaboration with our partners," explains Van der Geer. Ensuring effective communication throughout the supply chain is integral to optimise the use of these emerging technologies as well as preventing problems from occurring.

The key to connectivity

MSD has worked on a several projects in this area, which have not always been straightforward. "UNICEF mentioned that there were difficulties reaching people in need after natural disasters and disease outbreaks, and asked us, as an industry, to help them," explains Van der Geer. "The biggest challenges are connectivity and ensuring product integrity. We don't know where our materials are and we lack temperature control. We cannot guarantee that a quality product is delivered because we are shipping in-the-blind most of the time."

To address these difficulties, MSD turned to drones. "We created our own asset management platform, we created our own connected container and we executed a number of proof-of-concepts," says Van der Geer. "We flew products to clinics, to an offshore island off the coast of Puerto Rico and recently we executed long-range, fully autonomous and beyond line of sight trials in the Bahamas, including -70°C dry-ice deliveries."

The drones provided valuable insights about the drugs being shipped. "We could see the products in real time, where they were, what the conditions were, when it was delivered and when the container was opened," explains Van der Geer. "You get a lot more visibility in your supply chain. It was a good test ground to try out smart packaging."

The future is digital

Although such projects are hugely exciting, smart packaging is just one piece of the puzzle at MSD. "The longer-term strategy for us is not only using IOT-connected devices like drones," says Van der Geer. "We use these as a stepping stone to the future where we are looking to digitise the whole supply chain."

The vision, rather paradoxically, involves both scaling-up and drilling-down. "There are a lot of monitoring devices that you can buy off the shelf to track shipments but we want to be able to track each individual pallet, each individual parcel, each individual package and insure full product integrity at delivery," explains Van der Geer.

This level of precision allows for problems to be addressed efficiently and effectively. "The whole driver for us is to make sure that we can actually release products on a partial level and distinguish between each individual parcel," says Van der Geer. "If there is a temperature excursion, you may actually be able to save the majority of the shipment because it wasn't impacted, whereas if you only

100 years

MSD has been active in the Netherlands for almost a century.
MSD

track a full shipment, you can't do this." Despite the value of such data, accessing it is not easy. "The IoT devices that are available on the market today are mostly track-and-trace focused devices, controlling your shipment and supporting planning parameters," explains Van der Geer. "Another category of devices out there are used to validate the quality of the products when it is received by a customer. Making a bridge between those two is difficult but not impossible."

Achieving greater visibility of the supply chain is particularly important because of the shift in MSD's portfolio. "There is a move towards more biologics, more life-saving drugs and high-value products in smaller volumes, which means we need to think differently in terms of how we protect shipments," says Van der Geer.

Of equal importance

Being able to address problems that arise during shipment is important but Van der Geer emphasises that this is not the ultimate goal. "The data management itself makes shipment intervention possible; with IoT you have the ability to intervene before events occur, although I don't think that is the right element to focus on," says Van der Geer. "Actual shipment intervention is complicated and involves many direct communication lines and handovers. The ability to better understand the risks and capabilities, and be predictive and proactive are equally important."

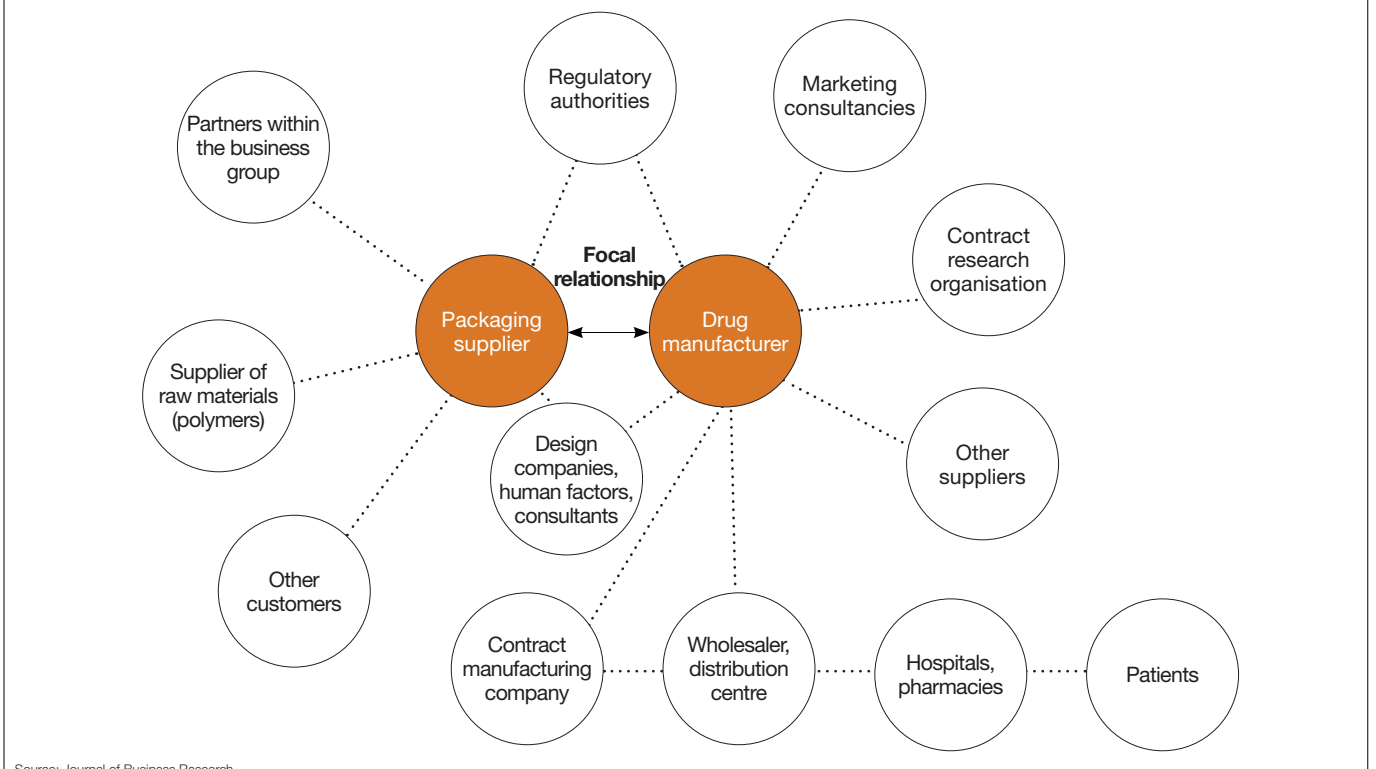
With this in mind, MSD is investing heavily into technologies and processes within the next few years. There are a number of different sources of information that MSD will draw upon in its efforts. "When we have our planning data, our transportation data and our temperature data, we can start bringing those together within the cloud environment," says Van der Geer. "What's next after that, is building predictive analytics, finding external data sets that we can use, as well as linking up with product serialisation data. We want to integrate all that information to get a large picture." ●

MSD in the Netherlands

- MSD is one of the pharmaceutical companies that invested the most in R&D: for 2017 it was 25% of the turnover.
- A number of important MSD medicines have been discovered and (partially) developed in the Netherlands, among these is immunotherapy for the treatment of cancer.
- MSD Netherlands is a pioneer in biological R&D for animal health; for example, the development of vaccines against upcoming animal diseases such as bluetongue in cattle.
- MSD Netherlands is the birthplace of many new developments in the area of fertility and contraception.
- By producing over 100 different veterinary vaccines and medicines, MSD Netherlands contributes to the prevention and the health protection of animals. The worldwide supply is over 50 billion doses per year.
- MSD invests in new production technologies such as Sphereon: a technology that freeze-dries live viral vaccines as easily soluble pellets.

Source: MSD

Relationships in pharmaceutical packaging innovation



Source: Journal of Business Research

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The revolutionary future of glass packaging

A world-leading innovator in material science, **Corning** has developed a solution to the glass packaging issues facing the pharmaceutical industry.

Sterile manufacturing for today's pharmaceutical industry is complex. Advances in drug delivery such as the rapid growth of biologics to treat chronic disease, advances in manufacturing including high-speed filling lines and the rising standards for quality necessitate innovation in glass packaging. The needs of the industry have evolved beyond current container capability. It is time for parenteral packaging to evolve to meet those demanding needs.

While glass is ideally suited for parenteral packaging, glass-related quality issues associated with conventional borosilicate packaging have plagued the industry for decades. Regulatory bodies and pharmaceutical manufacturers alike are well aware of the issues associated with current container failures. In 2011, the FDA issued an advisory focused on the need for package innovation to prevent glass delamination. In addition to the risk delamination poses to drug sterility, cracked containers and glass particulate contamination are also concerning. These glass packaging-associated events are some of the leading causes for drug product recalls and can lead to drug shortages that prevent critical life-saving therapies from reaching the patients who need them.

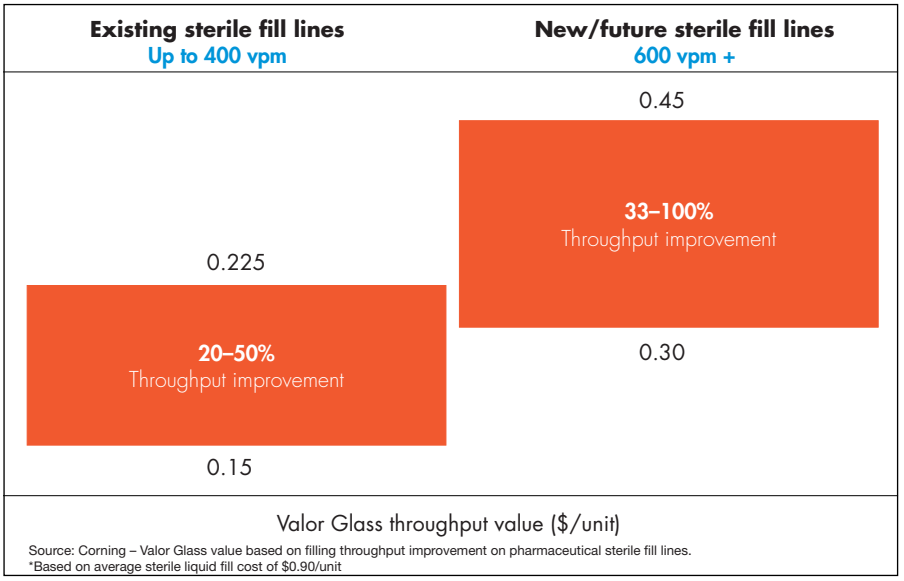
Manufacturers need a robust chemically durable container that improves quality, helps protect patients, and is specifically designed to survive high-speed fill and finish processing. Conventional borosilicate glass is being pushed beyond its capabilities. Despite its limitations and challenges, manufacturers continue to rely on borosilicate glass to deliver medicines to those in need for lack of a better alternative.

The answer to the pharmaceutical packaging industry's problem

In response to the FDA's call for innovation, Corning, a leading glass and material science company, leveraged its core capabilities to develop a solution specifically designed to address glass quality issues and improve pharmaceutical efficiency for sterile drug manufacturers. Corning's new Valor Glass, specifically developed for pharmaceutical use, improves the quality of packaging for injectable medicines and lowers costs for manufacturers by increasing capacity throughput and yield.

This revolutionary new packaging offers improved overall extractable and leachables performance and stronger hydrolytic resistance versus conventional borosilicate packaging. Its uniform surface chemistry and chemically durable drug contact surface makes Valor Glass ideally suited for sterile, injectable medicines. But the benefits to this all-in-one solution do not stop here.

This purpose-built glass is engineered to address several long-standing issues affecting parenteral glass container quality. Valor Glass eliminates delamination, prevents cracks, dramatically reduces glass particulates, resists damage and breakage and improves manufacturing throughput.



Source: Corning – Valor Glass value based on filling throughput improvement on pharmaceutical sterile fill lines.
*Based on average sterile liquid fill cost of $0.90/unit

On average, pharmaceutical companies see a >20% improvement of throughput demonstrated on new and older filling lines, which translates into an estimated fill cost savings of over $0.15 per unit. Additional value is created through improved yield, incremental sales and manufacturing agility.

Over the past two decades, the pharmaceutical industry has seen incredible advancements in the development of new drug therapies while the glass charged with protecting them has remained largely unchanged. 21st-century drugs require 21st-century glass. Valor Glass is currently being used in clinical trials, and several major pharmaceutical companies are working towards its adoption for previously commercialised drug products. The future of parenteral packaging may indeed be a filling line no longer constrained by glass. The efficiency gains with Valor technology on new and older filling lines could be the start of a manufacturing paradigm shift for the industry. ●

For further information

www.corning.com/valor

Risk versus reward

For parenteral drug products, there is a need to further investigate the materials that will be in contact with the drug product during manufacturing, storage, final packaging or the delivery of the drug to the patient. Jim Banks speaks to **Carsten Worsøe**, principal scientist at Novo Nordisk, about what is needed to better mitigate risk and optimise documentation for extractables and leachables.

In the pharmaceutical industry, patient safety is paramount. Eliminating the risk of contamination of products is therefore the focus of intense research. In an age when single-use systems have been widely adopted for parenteral drugs, there is an increasing need to ensure that during the production, storage, packaging and delivery stage nothing comes into contact with the drug that could cause harm to the patient or alter the formulation of the drug.

Since the late 1990s, extractables and leachables (E&L) have been carefully examined by the industry, in close collaboration with its packaging and equipment suppliers. Extractables – chemical entities that will extract from the components of a process system into a solvent under controlled conditions – help to identify potential leachables, which can migrate into a drug product over the course of its life under normal conditions. The field of study began with cases of pure red-cell aplasia (PRCA) for some of the patients taking Johnson & Johnson's Eprex. Since then, it has become essential to ensure E&L do not interfere with drug product assays or medical diagnostic tests, react with drug products components, create impurities or, in extreme cases, toxicity.

Carsten Worsøe, principal scientist at Novo Nordisk, has spent the past 20 years at the company developing analytical methods for E&L testing of new packaging and container closure systems. Having been involved in this field of research since its birth, Worsøe has witnessed major changes in testing procedures and technology for packaging and container closure systems that have advanced the field enormously.

In 1999, the FDA released guidance on the documentation for E&L for container closure systems, which also happened to be the time that Worsøe joined the company. "The company wanted someone who could do trace analysis to detect migration into drug products," explains Worsøe. "In the industry, it has become clearer what we need to do in terms of testing, but the FDA guidelines give us little help. In Europe, the

plastic immediate packaging material guideline from 2005 also has little guidance on how to do E&L documentation."

Time to keep pace

It is clear that regulation has not kept pace with change occurring in the industry and Worsøe has some solutions.

"We have proposed that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) should take up a guideline on E&L," Worsøe says. "It would help if everyone were working to the same standards. What we find is that some national health authorities are very interested in E&L, while others are not interested at all."

The lack of interest among some health authorities may, in part, be due to the fact that very few problems have occurred over the years. That is no guarantee that the same will hold true in the future, however, as new packaging materials, designs and new drug formulations come to market.

It is imperative that preventing contamination remains high on the agenda, particularly in the single-use market.

"One of my priorities is examining the potential outcomes of leachables interacting with drug products, especially within biological drug products where leachables can react with individual amino acids and potentially change the quality of the drug," says Worsøe. "There is more research being done into the safety side – looking at the safety of the leachables when administered to patients – and that area is well funded."

Change on the horizon

The industry is also beginning to put more resources into looking at potential changes in drug product quality. "Many contract labs do analytical testing and documentation, and they are now also working on providing safety assessments for leachables," Worsøe says. "Few are also looking at the potential for biological interaction."

While regulation has been at a standstill for most of the past 20 years, changes in analytical methods have also been relatively slow. Orthogonal methods are the foundation, though no single method can be used to detect all extractables. Liquid and gas chromatography, inductively coupled plasma mass spectrometry (ICP-MS) and a range of other options, including total organic carbon analysis or gravimetric analysis mass of non-volatile residue (NVR), must be used in various combinations to get a full spectrum of results.

What has changed, however, is the way in which the results of these detection methods for extractables are managed. As in many industries, data is the key. "Now, the real change is on the data side," says Worsøe. "The data is being evaluated by computer, rather than manually and there are more high-resolution mass spectrometry instruments using accurate mass detection that yield much more information. We are developing databases for the accurate identification of previously unknown leachables. Sophisticated algorithms are enabling us

Regulatory guidance, guidelines and legislative directives	Standards
FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. Chemistry, Manufacturing, and Controls Documentation (1999)	ISO 10993 Biological Evaluation of Medical Devices
FDA Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry Manufacturing and Controls Documentation (1998)	ISO 11040 Pre-filled syringes
FDA Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (2005)	ISO 11979 Ophthalmic implants
FDA Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators (1998)	ISO 14971 Application of Risk Management to Medical Devices
FDA Guidance for Industry and FDA staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)	ISO 15747 Plastic containers for intravenous injections
EMA Guideline on Plastic Immediate Packaging Materials (2005)	ISO 20072 Aerosol drug delivery device design verification – Requirements and test methods
EMA/Health Canada Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (2006)	ISO 27427 Anaesthetic and respiratory equipment — Nebulizing systems and components
Commissiom regulation (EU) 2015/174 amending and correcting Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. Journal of the European Union. 6 February 2015	USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 93/42/EEC concerning medical devices	USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/ Delivery Systems
CFDA Technical Guideline for Compatibility Studies between Chemical Drug Injections and Plastic Packaging Materials (2012)	

Source: Regulatory Toxicology & Pharmacology

"One of my priorities is examining the potential outcomes of leachables interacting with drug products, especially within biological drug products where leachables can react with individual amino acids and potentially change the quality of the drug."

Eliminating the risk of contaminating products is of utmost importance to the pharmaceutical industry and its patients.

to look at the data packages, and that is driven by the technology providers with which we work."

These developments have already made a big impact but Worsøe is keen to continue driving progress forward. "The next step is to build libraries using liquid chromatography, as we already have standardised libraries for gas chromatography," says Worsøe. "The processes for analysis have improved a lot, especially for the characterisation of unknown leachables."

Collaborate for clarity

Effective risk mitigation relies firmly on the successful cooperation between the different internal disciplines as well as between the pharmaceuticals company and its suppliers. Within Novo Nordisk, Worsøe has been one of the main facilitators in this area, bringing together relevant people in packaging materials, toxicology, formulation, regulation and analytical chemistry to participate in risk assessments and strategies for E&L testing in development, and supply projects within parenteral delivery systems – including pre-filled cartridges, pre-filled syringes and pump infusion systems.

"Within the company, we must also have people who understand CCS, SUS, analysis, toxicology and many other aspects."

"Collaboration starts with having a good relationship with suppliers of container closure systems (CCS), single-use production systems (SUS) and device parts," says Worsøe. "The key to that is a confidentiality agreement, which must be in place as the foundation of the relationship. This is because there are relatively few suppliers in the industry and they each work with many pharmaceutical companies." Good internal working knowledge is also key. "Within the company, we must also have people who understand CCS, SUS, analysis, toxicology and many other aspects," says Worsøe. "They all play a part in enabling us to set up studies to see what we can extract from a component, so that we can then look for them as leachables."

For now, the onus is on the pharmaceutical company to identify E&L risks and document them in a way that – although not strictly defined by regulatory bodies – is an acceptable description of the E&L analysis and any potential risks.

For Worsøe and others, this approach needs to evolve to reflect the collaborative nature of the industry. "Today, various industry groups are trying to get container, and CCS and SUS suppliers to provide extractables data with their components," explains Worsøe. "One example is the BioProcess Operation Group (BPOG) E&L SUS team where approximately 15 pharma companies and 12 major SUS suppliers are working together in defining and providing supplier SUS extractables data to be used directly at the pharma companies."

On the right path

This is an important step forward in reducing the time and effort required by each pharmaceutical company. In addition, such activity can provide valuable guidance for suppliers about which extractables data is relevant and how it is used.

There is an ongoing debate about what constitutes an appropriate level of information that should be provided by suppliers and about what testing should be done. Some proposals have been made and organisations such as the Extractables & Leachables Safety Information Exchange (ELSIE) and others, are making a significant effort to advance this debate.

Some suggestions have, so far, been seen as too wide-ranging to garner consensus, but they have served to move the debate forward. A key step in clarifying this discussion and in advancing the approach to the risks of E&L in general, would be to give the industry a clearer idea of the documentation process.

"The priority remains setting guideline standards for E&L documentation," Worsøe says. "My hope is that an ICH guideline on E&L will get us on a common ground between health authorities, pharma companies and suppliers."

With clarity, collaboration and continued advances in data analysis, E&L risk mitigation will become simpler and quicker, leaving the likes of Worsøe free to explore further into the realm of unknown leachables.

Elastomer manufacturing: primary packaging for parenteral drugs

With the advent of biologics and highly sensitive drugs, primary packaging materials must meet the highest-level of functional, regulatory and cleanliness standards to ensure compatibility and ultimately, patient safety. Rahul Thakar, PhD, discusses **Datwyler**'s solution to these ever-stricter requirements is their highest-quality manufacturing standard, First Line.

The manufacturing concept of First Line adopts a quality-by-design (QbD) approach that begins with a fundamental question; if the common denominator is defined by the primary packaging material, should not the primary packaging environment be an extension of the drug manufacturing environment?

Before First Line's commercialisation in 2009, Datwyler collaborated with pharmaceutical and biotech clients to understand the needs of the market. To address the unmet market needs for the highest-quality components, it was important to redefine the manufacturing concept that was determined by Datwyler and challenged by industry experts. A decade later, it can be said with confidence that the concept is the new standard with the opening of the third First Line facility in Delaware, US.

Packaging challenges for complex and sensitive drugs

It is important to consider the QbD approach for the product first and extend it into the manufacturing environment. Highly sensitive drugs demand modern elastomer compounds with the cleanest extractable and leachables (E/L) profile, and are highly sensitive to foreign contamination. To meet these product challenges, Datwyler has developed best-in-class rubber compounds, such as FM457, which is widely recognised as the cleanest elastomer in the parenteral packaging space from an E/L standpoint.

Silicone, which is a necessary evil, is needed for machinability, functionality, and transportation of elastomeric products. Silicone also has a tendency to migrate into drug formulations. To mitigate risks against silicone sensitivity, Datwyler has developed the proprietary Omni Flex coating that eliminates the need for siliconisation. Omni Flex has been commercially successful with several drugs on the market that benefit from this fluoropolymer technology.

The First Line manufacturing concept starts with a 'zero defect philosophy' in mind. To achieve this, the smart facility design regulates personnel, material flow, and waste flow. The critical processes are automated to eliminate or minimise operator contact. Here, statistical process controls with continuous monitoring of products aim to minimise defects. Automation enables the entire production floor to be paperless, this is essential since cellulose is the largest contaminant in parenteral drugs. Finally, continuous improvement efforts are defined by process FMEAs and poke-yoke principles so as to build quality into the process. As a second line of defence, components can be vision inspected at a per-piece level for cosmetic and dimensional defects.

More stringent expectations of the regulatory authorities

Data suggests that authorities' expectations are becoming more stringent, pushing our industry to reach higher quality levels. It can be agreed that these trends on stricter expectations from the pharmaceutical companies, as mandated by the regulatory bodies, are here to stay, and will only get stricter. It is only a matter of time that this will be the 'new normal' within the industry. To meet these challenges, Datwyler pioneered the First Line manufacturing concept much ahead of its time. Strict specifications for particulate levels and continuous improvement efforts are in place to strive towards our goal of zero defects. This QbD approach is at the centre of the First Line concept.

Globalisation and supply chain optimisation

Pharmaceutical companies maintain a global manufacturing presence to provide drugs into several geographic regions and regulatory environments. It is expected that component manufacturers are able to match that global footprint, and have an understanding of the complex regulatory landscape.

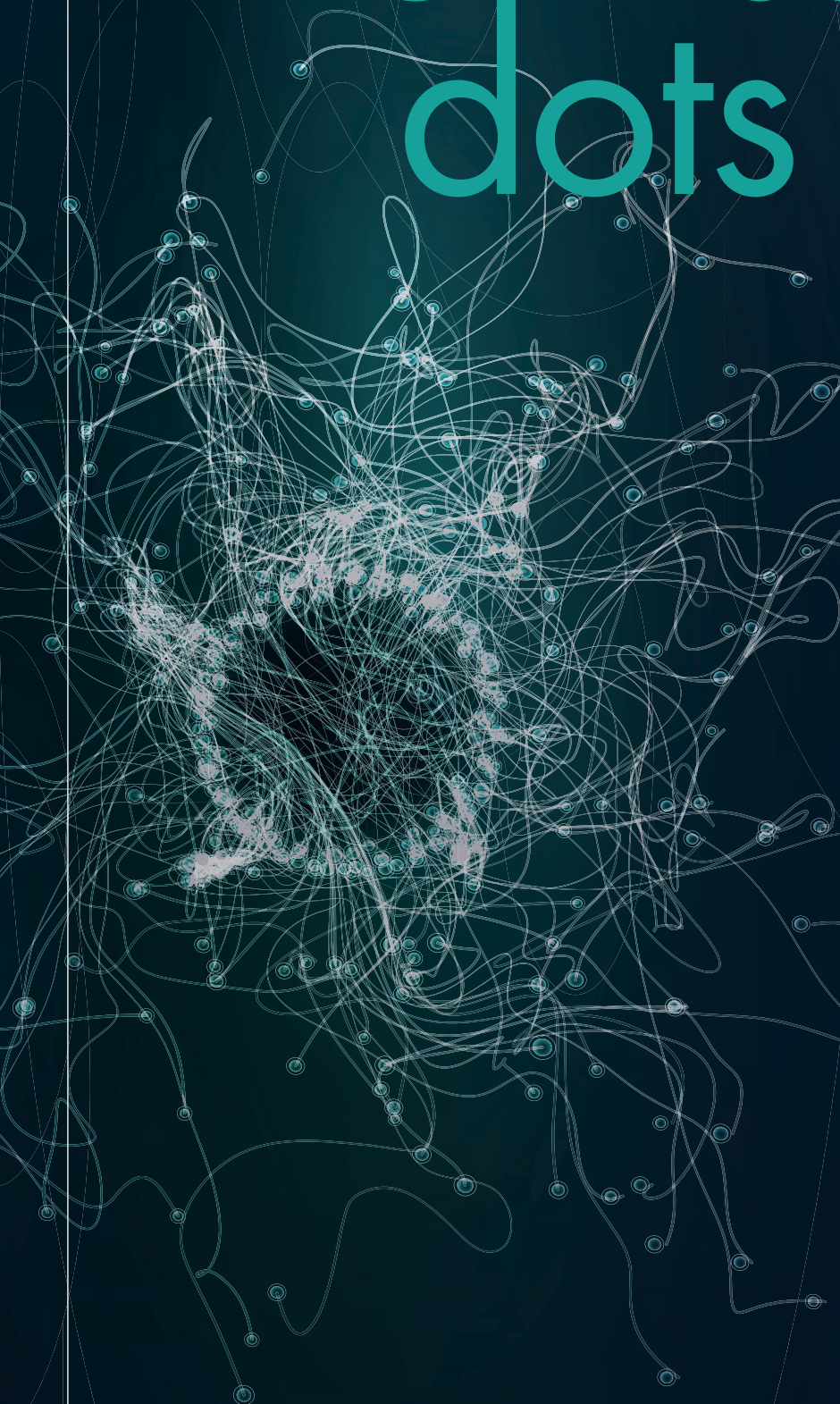
For pharma and biotech clients to leverage a global manufacturing footprint, the First Line plants in Belgium, India and the US utilise the same raw materials, technologies, processes and produce pharmaceutical components with the same specifications. As a result, this risk mitigation strategy enables business continuity and supply chain, which is a key consideration in today's pharmaceutical manufacturing landscape.

By implementing a QbD approach when developing the First Line manufacturing standard, Datwyler has set the bar for high-quality parenteral packaging manufacturing. ●

For further information

www.datwyler.com

Connect the dots



AI is set to play an increasingly important role in the pharmaceutical industry, providing life science companies with faster, more efficient ways of uncovering drugs, sourcing data and responding to regulatory challenges. Will Moffitt speaks to **Joerg Stueben**, senior expert of global regulatory operations at Boehringer Ingelheim, about the implications of the technology.

In 2018, graduate student Na le Dang made a groundbreaking discovery. A student at Washington University School of Medicine, Le Dang had been experimenting with machine-learning techniques, looking into the way certain drugs are broken down at a complex molecular level.

Her attention had been drawn to the fungal agent terbinafine, a drug that had been previously associated with several deaths from liver failure, with past researchers attributing these fatalities to a toxic compound named TBF-A in 2001. The problem was, nobody quite knew why this particular drug became poisonous once it entered the liver.

By creating an algorithm to analyse the deconstruction of these molecules, Le Dang was able to decipher the complex patterns bubbling away beneath the surface, identifying that the metabolism of terbinafine to TBF-A was an intricate process, where the compound was formed only after the first metabolic step had occurred.

While Le Dang's discovery represented a small, but pivotal, step towards eradicating future deaths induced by terbinafine, from the perspective of the wider pharmaceutical industry, it could be a giant leap – a powerful demonstration of the potential for machine-learning techniques in spotting patterns in compounds that routinely eluded even the most experienced researchers.

Naturally, this ability to collate and analyse complex forms of information in large quantities makes AI an exciting and potentially transformative resource for life science companies, aiding data management and research departments that are frequently under-staffed and under pressure.

AI's ability to gather and analyse complex data makes it an exciting resource for life science companies.

For Joerg Stueben, a senior expert of global regulatory operations at Boehringer Ingelheim, it is these analytical capabilities that make the technology such an exciting prospect.

"AI can see things that some humans can't," Stueben says. "The power of this technology lies in its ability to order and interpret huge amounts of information in meaningful ways."

Steuben has been working in regulatory operations for 24 years, starting off as deputy head of quality control for Lipoid in 1995. In his current role he is responsible for compiling and submitting detailed product records to health agencies, ensuring these reports comply with legislation in specific regions.

While historically, regulatory operators would be working with a photocopier, sending pallets of reports all over the world and waiting for lengthy periods for feedback from various health agencies, these days submissions are filed much more quickly.

For Stueben this means regularly sending detailed product information to the European Medicine Agency's centralised database, the EudraVigilance Medicinal Product Dictionary (EVMPD) and ensuring that reports comply with the Identification of Medicinal Products (IDMP) initiative. Recently passed laws on data transparency mean that these departments are being called upon to present product details in a more standardised and structured way.

A chance for success

It's no secret that, for many pharmaceutical companies, getting drugs to market is tough. As a recent study by Tufts Centre (CSDD) for the Study of Drug Development shows, the success rate for developing new prescription medicine stands at 12%.

To enhance their chances of success, drug companies are experimenting with AI and machine learning to try to glean insights from enormous quantities of data at their disposal.

Whereas an experienced regulatory expert might have up to 10 past submissions to draw from, public journals and cuttings, along with agency databases, yields thousands of previous reports – the online database PubMed, for example, currently has 30 million citations on biomedical literature, all of which can be drawn upon to provide a greater understanding of chemical compounds and patient reactions. At a time when staff numbers are low, but quality research is paramount, AI is being touted as a way to use company assets more efficiently.

"The time-saving capabilities are huge," Stueben says. "A person who needs to check and read documents for about two weeks can receive the same meaningful information in about 10 minutes. Ultimately, that means our researchers are not spending valuable time reading articles that turn out to be useless."

Natural language processing (NLP) is also providing researchers with a handy way of collecting unstructured data such as physician's notes, pathology reports and electronic medical records, extracting insights on the properties of certain drugs and their efficacy.

This coincides with a broader move to leverage real-world data, and harness information outside clinical settings, such as health records, disease and product registries, billing data, and information recorded on health monitoring devices.

Amgen has been successful in this department, gaining approval for a form of cancer therapy based on a single-armed phase-II study, supported by evidence derived from medical records.

For Steuben, these tools offer the opportunity to extract information from health authorities, gathering regulatory intelligence on specific therapeutic areas and analysing the regulations in particular countries.

"Typically, authorities will come back with follow-up questions, which we have a very limited time to answer," says Steuben. "Not only are we working on

12%

Success rate for developing new prescription medicine.

Tufts Centre

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responding to those questions more quickly, but trying to avoid those questions in the first place."

With investment in machine learning increasing and breakthroughs of this magnitude gaining more traction, it is inevitable that AI is going to reshape the research and development aspect of the pharmaceutical industry. Even so, teething problems still remain.

A recent study by the CSDD and the Drug Information Association (DIA) shows that integration and technical knowledge present key challenges. Undertaken with eight pharmaceutical and biotechnology companies, the survey revealed that a lack of skilled staff, data structure and budgets constrained initiatives to successfully implement machine-learning algorithms. It concludes that regulatory constraints and data silos remain significant issues for the pharmaceutical industry that must be overcome to enable more sophisticated AI programs.

For Stueben, regulations around how to use the technology are a key area that needs to be addressed, particularly as the technology becomes more prevalent.

"On the whole, the industry needs to work more closely with regulators to come up with a framework of approval and guidance that is safe and rigid enough to enable these kinds of technologies," he says.

In April, the US Food and Drug Administration (FDA) released a white paper proposing a regulatory framework to decide how medical products that use AI should seek approval before they go on the market, welcoming feedback on the document. So far the agency has only given the green light to devices where algorithms are frozen – meaning that they do not change each time an algorithm is used – but instead are changed by a manufacturer.

However, such regulations are not suited to algorithms with self-learning capabilities that continuously evolve, learning from past mistakes, to become more efficient.

Naturally, a key topic of discussion is how to deal with the so-called 'black box' problem in machine learning. In a field built on trust and transparency, the inability for advanced algorithms to show a clear thought process behind decisions is perhaps the most troubling aspect of AI application across the board.

"Ultimately, in the pharmaceutical sector, AI will gain further implementation not only because it outperforms humans at certain tasks, but because authorities can decipher when it works and why," he says.

While the FDA and other government bodies continue to look into these quandaries, naturally the most influential developments will come from outside of the political sphere. In May, for instance, a team from Google Brain released a paper entitled 'Human-Centred Tools for Coping with Imperfect Algorithms During Medical Decision-Making'. The paper examines an algorithmically powered user interface to manage the uncertainty of medical image classification to guide better decisions with uncertain predictions.

For now, the adoption of AI and the willingness to experiment with the technology by larger pharmaceutical companies, coupled with an increase in precision medicines and a move to harness real-world data, means that the technology is set to shape various areas of pharmaceutical research and development in the future.

In a field where roughly 90% of drug submissions fail to make it to market, where budgets are being slashed and clinical trials are costly, many pharmaceutical companies are hoping that the next blockbuster drug lies hidden in a data lake – a problem that human intuition alone cannot solve.

A helping hand

Egorov Artem/Shutterstock.com

Since 1997, pharma has been looking at additive manufacturing (3D printing), trying to understand what role it will play. Its value is clear, but to pinpoint where it should be used best still remains a challenge. Andrew Tunnicliffe speaks with **Professor Clive Roberts**, head of the School of Pharmacy at the University of Nottingham, and explores the possibilities.

When it was announced that MIT Professor Michael J Cima and several colleagues were working on a technology that represented "a new way of formulating drugs with unprecedented dosage control", it was likely not envisaged that, more than 22 years later, it was still finding a significant place in pharma. The team at the Department of Materials Science and Engineering used 3D printing to construct tablets using pharmaceutical-grade materials. ▶

Water-based 3D inkjet printing

Solvent inkjet printing has been used to 3D print free-standing tablets from a water-based formulation. Using water-soluble PVP ink-based and thiamine HCl as a model API, a printable ink was developed using polysorbate 20 and glycerol as additives. Appropriate surface tension and viscosity values were measured and optimum print parameters were investigated.

Through the initial printing of up to 10 layers, it was observed that two phase separation processes occur: one as a function of time and the other related to the number of layers printed. Optical microscopy imaging show the thiamine HCl crystals exist as a suspension in PVP. Combustion analysis confirmed the successful translation of the composition of the ink into the printed tablet, which contained thiamine HCl in the ideal NSH polymorphic form distributed uniformly throughout the formulation.

Given the high solubility of the API and polymer excipient, drug release was rapid to such an extent that it was not possible to control it by varying the 2D pattern and number of layers. However, this process used no toxic materials, did not need extreme conditions (for example, high temperatures), nor used secondary printing methods to produce a wholly inkjet-printed tablet, without incorporating an edible substrate that would require cutting and encapsulation. The ink formulated in this investigation can potentially be used as a 'universal' pharmaceutical formulation for any water soluble API. Investigation of the tablet's mechanical properties (such as hardness and friability) should be conducted to better characterise the handling and physical integrity of the tablets.

Source: *International Journal of Pharmaceutics*

Today, the industry is still looking at how best to deploy that technology in any meaningful way. Of course, there have been successes; in 2015 Aprecia Pharmaceuticals became the first company to be awarded US FDA approval to produce a 3D-printed pharmaceutical. Spritam, a reformulated anti-epileptic medication, has a porous structure, which means it dissolves and delivers a very high dose within a few seconds of being in contact with saliva. This helps to address dysphagia among patients, particularly the young and old.

"If you look at the way medicines are now being distributed, there's a clear shift away from going to your local pharmacy."

However, despite much investment in R&D, the manufacturing process arguably remains on the threshold of something big in pharma, with great promise but not the mass application Cima and the team likely believed it would achieve. In medicine more generally, however, the technology has already gained a significant foothold by being used to develop implantable medical devices and now, increasingly, in dentistry.

"The Aprecia story is an interesting case study," says Professor Clive Roberts. "As anyone should in this kind of sector, what you really need to start with is a clinical problem and what would be a good formulation, dosage solution for that. What makes the Aprecia product interesting is that the process of manufacturing they used gets them a tablet that dissolves very quickly in minimal liquid. That would not be possible to achieve using standard fast-melt approaches. So there's a good reason why you would adopt that technology to make that product; it gives you a certain clinical outcome."

The real question

Roberts is head of the School of Pharmacy at the University of Nottingham. With a background in pharmacy over the past three decades that covered, among other things, formulations, new medicines and biomedical devices. "I would say 3D printing, at the moment, is at the stage where a lot of people have shown that you can make many different types of dosage forms," says Roberts. "But the real question is, what is the clinical need and business need?"

It is a fair question given the nature of additive manufacture, where the cost of production is not determined by the size of the production line. Roberts says, unlike more traditional Western manufacturing processes, where the cost per unit falls as you scale up, 3D printing costs remain essentially the same whether it is one or 1,000 units produced. It is largely for that reason, Roberts believes, the future of mass additive manufacturing, in pharma at least, is a long way off. "It certainly won't become the norm for standard medicines," says Roberts. "There's no obvious clinical reason for why that would be needed."

However, it seems it does have a future, evident in the investment from the likes of GlaxoSmithKline (GSK). The global powerhouse has had a leading role in the development of 3D printing strategies for some time, investing heavily in research looking at how it can utilise the process to support future innovations. As far back as 2016, the company's director of technology, Martin Wallace, had acknowledged the mass manufacture challenges presented by additive technologies. "Current technology allows us to produce up to 1.6 million tablets per hour," Wallace told Redshift. "You're going to need a lot of printers to achieve that sort of production."

GSK, therefore, is more focused on the other ways it can use additive manufacturing, including R&D for new drugs and digital compounding, an area that has big potential. "There are some significant advantages if 3D printing was used in clinical trials," Roberts explains.

Beneficial 3D printing

Much of the heavy work carried out by a compounding pharmacist could be done by an additive process, eliminating the need to hand produce numerous iterations of a trial drug. "It is essentially just using another tool to compound so I don't see any blocking issues," says Roberts.

The advantages of additive manufacturing in the clinical trial setting do not stop there. It could also

help speed up the process, allowing drug companies to produce small amounts of the same drug easily and quickly, responding to reported outcomes more efficiently by altering compounds or changing them altogether. "I think in terms of application and where we'll see it emerge first," says Roberts, "It is almost certainly going to be in clinical trials manufacturing, where compounding pharmacists could run 3D printers in a small manufacturing facility to make dosage forms in the hundreds or thousands."

This proposition highlights another area where additive manufacturing could bring significant benefits, for both the pharmaceutical and healthcare sectors. The ability to produce unique and tailored dosage forms in smaller runs makes it attractive to pharma – as well as clinicians and patients – by offering the potential to personalise medicines to an individual's needs.

"Personalisation could include different APIs (active pharmaceutical ingredients) at different concentrations," says Roberts. "Each of those APIs could have different release profiles. So you could look at the metabolic processing rate of those individual patients and adjust the amounts. You could change the distribution of the drug and the dosage form to get different release profiles too."

However, it is important to distinguish between possibility and optimality. "All these things are, to be honest, technically not that difficult to achieve," says Roberts. "It's a question of whether there's actually a clinical need for such personalisation."

The revolutionary suggestion

Perhaps, however, the more exciting and potentially revolutionary suggestion is distributed manufacturing. Having the ability to manufacture medications away from a centralised facility is a real possibility thanks to 3D printers. Roberts says it is easy to imagine a printer in a pharmacy and even in a patient's home, producing tablets. "That kind of idea is essentially digital compounding," says Roberts. "So a compounding pharmacist or pharmacist who's able to make medicines could use a 3D printer to make a medicine closer to the patient."

Labelling it the 'Amazonisation' of medication delivery, this is already starting to occur, albeit at a low level. "If you look at the way medicines are now being distributed, there's a clear shift away from going to your local pharmacy," says Roberts. "People are consulting health professionals and ordering things online. In the long term, as the technology matures, it's not unreasonable to think about having some kind of 3D printer, not under control of the clinician, but in people's houses or pharmacies. Why not?"

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Using pharmaceutical-grade materials, 3D printing can be used to construct tablets.

Such a method of delivery has real benefit, not only for efficiency but for personalised healthcare. If this is to happen, regulators need to address the challenge of allowing decentralised production in a safe way, something that currently doesn't exist.

This is not insurmountable, however. "Over time pressure will start to influence the regulatory environment," Roberts explains. "Regulations change, it takes a long time but they do shift," says Roberts.

"What makes the Aprecia product interesting is that the process of manufacturing they used gets them a tablet that dissolves very quickly in minimal liquid. That would not be possible to achieve using standard fast-melt approaches."

At present, the industry is going through what Roberts terms "that normal cycle", where there is a lot of interest but little action.

"The reality of actually producing products that make money is going to bite," warns Roberts. "Then there's consolidation, when people think 'okay, can we do something that's more transformative to the industry rather than just looking at niche areas?'"

Additive manufacturing is not going away anytime soon but pharma is not going to be revolutionised overnight. It has huge potential, particularly in clinical trials and personalised care, but identifying a clinical need and business is essential in order for real progress to happen.

1.6 million

Current technology allows for production of more than one million tablets per hour.

GSK

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Leak detectors are used for 'on-site' mobile leak detection, such as company premises, as well as for worldwide service jobs in a variety of different locations. Its leak detectors stand out above all due to their high performance combined with low weight.

The compact leak detectors are used first and foremost for stationary applications to detect leaks and test for leak tightness. They are also portable thanks to a special leak detector cart. Compact leak detectors are used in a wide range of industries, from applications in heavy industry right up to cleanroom applications. In the latter case, the dry versions of the leak detectors are being used.

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The ASM 340 leak detector from Pfeiffer Vacuum.

Multipurpose leak detectors

Multipurpose leak detectors combine performance and easy operation with the reliability that customers have come to expect. One such example is the ASM 340, a high-performance and durable leak detector for reliable quality assurance. The wide scope of application ranges from industrial and analytical applications to research and development, all the way to the testing of pharmaceutical blister packages. The compact leak detector can be used in serial production and maintenance tasks.

Qualitative localisation of leaks and quantitative integral or local inspection are possible with the ASM 340 leak detector. It impresses with its efficient vacuum system, which guarantees that it is ready for immediate operation. Furthermore, it distinguishes itself with a fast response time, due to the high helium pumping speed. These features lead to a short cycle time and high throughput. The ASM 340 is the only leak detector in its class on the market that is capable of locating leaks starting at 100hPa.

A large selection of interfaces enables easy integration into production lines. The removable manual control element and the optional sniffer probe with LEDs make the work that much easier. Measured data can be recorded and evaluated using an SD card. The wireless remote control enables operation from a distance of up to 100m. Thanks to the robust design and the minimal maintenance required, service costs are also reduced.

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Helium leak detectors are the ideal solution for leak detection and leak-tightness testing under vacuum. The test gas helium is safe and a small, light molecule that is suitable for detecting micro leaks. The detection range of helium in vacuum tests lies between 10^{-2} and 10^{-13} Pa×m^{3}/s. Helium leak detection is extremely accurate, quantitative and repeatable.

Manual sniffing or spraying is often the easiest way to detect a leak with helium. But it is also possible to use automatic leak detection solutions that are independent of the operator and provide a considerably higher detecting speed. The integral leak detection is designed to achieve predefined quality and component throughput levels.

The use of test gas leak detection methods has the bonus of delivering extra data compared with traditional leak detection methods such as bubble testing or pressure drop methods. This data can be used to improve production processes and successfully detect every leak. ●

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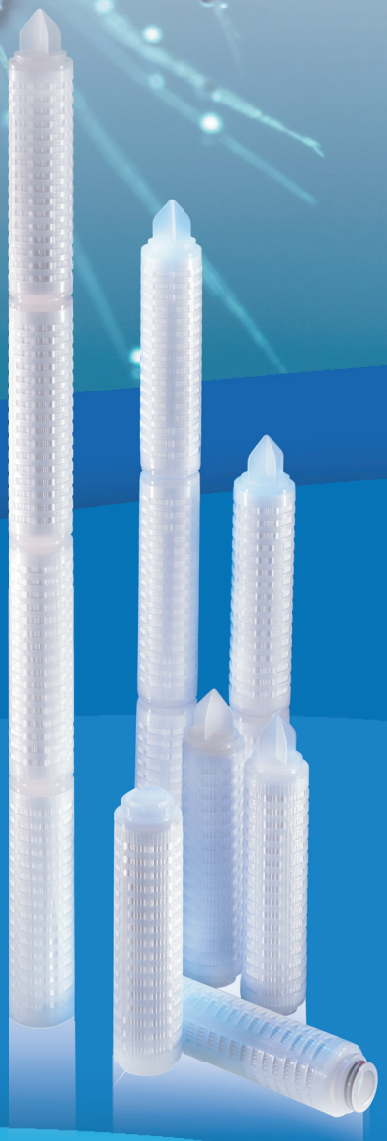

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The animal-free philosophy

World Pharmaceutical Frontiers gets the low-down on BEAPURE, **BEA Technologies**' new range of ethical, animal-free filtration products for the biological and pharmaceutical industries.

BEA Technologies researches and focuses on the development of products able to obtain high performance in the filtration carried out within the pharmaceutical industry.

New to the market: animal-free products freshly available

Recently, the company has launched its BEAPURE line of filter elements, which are completely animal-free products. To be animal-free simply means that any polymeric part or component used in production is without any trace of animal origin. After an extensive research and development phase the team at BEA was able to test then select only the purest polymers for the production of the filters. The line will incorporate filter elements in Nylon 66 membrane and positively charged Nylon 66 membrane, which is used to remove endotoxins or other fine contaminants negatively charged from WFI or other solutions.

Six steps to purer filtration

BEA recommends a six-step guide to consistently purer filtration, with the key points being:

- filters made of animal-free pure components and parts
- controlled original materials in compliance with the latest regulations
- periodical controls in a certified laboratory of extractables and leachables
- protection from external contamination during production
- easy and quick identification of materials to help operators ensure quality
- traceability of production through the barcode on the label.

Consistent experience: the promise to maintain company excellence

BEA Technologies tries to act as a global consulting supplier to enable clients to leverage filtration and separation activities to obtain safety and quality

"After an extensive research and development phase the team at BEA was able to test then select only the purest polymers for the production of the filters."

The products containing the Nylon 66 membrane also come with halal certification. The BEAPURE line also includes filter elements with PES and PTFE membranes, and a series of filters made by borosilicate fibres and nanofibres for highly effective filtration of viscous solutions in drug-manufacturing processes.

Together with filters based on polyethersulfone membranes, NYLON66+ completes the series of membrane cartridges adopted for liquid sterilisation and endotoxin removal in drug-manufacturing processes.

prescribed for the process, gaining a relevant cost savings.

The deep experience of BEA Technologies and implementation of the BEAPURE concept provide value and services to support customers processes to obtain highly safe products.

BEA Technologies has been an active presence on the filtration market for the past 50 years, working successfully worldwide in various sectors, including beverage, chemicals and pharmaceutical markets. The company manufactures a wide range of innovative and high-tech products to filter both solid particles and

The company offers solutions for the microfiltration of liquids and compressed gases dedicated to the specific needs of the biosciences industries.

microorganisms, removing them from liquids, air and gas. Internally, the company organisation enables it to guarantee reliable results, through its commercial and laboratory services (SLB).

Quality assured: dedication to maintain innovation

The headquarters in Pero, just outside Milan, is based on three facilities that occupy a surface area of 12,000m².

In the plant there are two cleanrooms where the company produces all its membrane filters and filter elements for use within food and pharmaceutical applications.

In 1994, BEA became one of the first filtration companies in Italy to get its quality assurance system certified in accordance with the requirements of the ISO 9001 standard. All filters are produced in a certified cleanroom, in a controlled environment that is monitored by computer systems to ensure that it complies with industry good manufacturing practice (GMP). ●

For further information

www.bea-italy.com

The first move

There is increasing talk of 'patient centricity' within the industry. Incorporating this concept into drug delivery can be challenging but provides huge opportunity to improve adherence. Louise Thomas speaks to **John Burke**, senior consultant at Team, about the best practices when implementing this approach.

Patient-centric drugs are widely recognised as being fundamental for optimising health and well-being in individuals. In addition to selecting the appropriate drug type and strength, the product design must also sufficiently address patient needs. This includes consideration of the disease, routes of administration, active pharmaceutical ingredients and drug delivery technologies. The latter has received less attention in the industry but forms a crucial element of patient centricity. Some have referred to patient-centric design as the 'next frontier' in drug delivery.

Despite the widespread discussion of the concept, a universal definition does not exist. For John Burke, a senior consultant specialising in

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parenteral drug delivery devices at Team, it is about the mentality. "Putting the patient and their needs front and centre, whether that is in the development of a novel drug or innovative delivery device," says Burke. "Ultimately, it's a shift in mindset; rather than developing medicines for patients we should challenge ourselves and ask how we can develop a therapy or delivery device in partnership with patients."

Stand out

There are a huge number of advantages in embracing the concept, both for patients and pharmaceutical companies. "It stands to reason that putting the patient at the centre should lead to therapies, devices and services that better meet their specific needs and capabilities," says Burke. "In an increasingly competitive marketplace, getting this right will make your product stand out."

This means embracing a collaborative approach. "Consider two competing biosimilars, which from a purely therapeutic standpoint are identical," Burke continues. "By working with patients to better understand their capabilities, challenges and concerns, we can offer a much improved user experience."

Small changes can make a big difference in this context. "This might be a small iterative change such as improving the quality and clarity of the information provided through the packaging or instructions for use," explains Burke. "Alternatively, it could involve tailoring the delivery device to meet the needs of challenging groups such as paediatric or geriatric patients with reduced physical capabilities or limited dexterity."

Ultimately, the idea is to think holistically about what it is that matters to patients and making adjustments accordingly. "The aim is to provide a better and more relevant product or service in order to deliver a great user experience," says Burke. "This may in turn lead to patient preference or improved compliance."

Navigate challenges

Adopting a patient-centric approach also involves navigating a number of various challenges. One of these is the distance from patients. "Early-stage R&D within pharma is traditionally quite disconnected from the realities and real-world experiences of patients self-administering therapies," says Burke. "This can lead to molecules being developed with little to no consideration as to how this can be consistently administered outside of a controlled clinical setting."

This separation is the norm in the industry, but it does not have to be. Companies are already starting to change their ways of working to facilitate better communication and collaboration with patients. "Increasingly we're seeing large pharma companies setting up user experience groups responsible for championing the end user within the organisation," says Burke. "They can provide invaluable insights from existing marketed products and patients, and feed this into early-stage drug discovery and development. Opening up these channels and lines of communication within large global organisations is challenging but early input from both clinical and user perspectives is critical in order to identify potential opportunities and maximise the benefits of a new therapy."

"Rather than developing medicines for patients, we should challenge ourselves and ask how we can develop a therapy or delivery device in partnership with patients."

There are certain drug delivery devices where it is particularly difficult to implement a patient-centric approach. One example is platform delivery devices, which are becoming increasingly popular within the industry.

"Putting your drug into a proven device goes a long way towards mitigating development risk, and can significantly reduce time to clinic and eventual commercial launch," explains Burke. "However, there are potential downsides to this approach as platform products offer limited opportunity for customisation or changes. In this case, tailoring the device to your patients may be prohibitively expensive in terms of cost and development time." ▶

Principles for increasing patient involvement in drug development

- **Acknowledge the importance of patient involvement:** define what it means to truly incorporate patients as partners.
- **Take inventory:** review existing efforts and work with patients to determine when patients should be more included.
- **Be transparent:** own up to instances when this could have been done better, both internally and to external stakeholders such as patients, payers and regulators.
- **Trust patients:** invest in them and take the time to educate them on issues and needs.
- **Involve patients continuously, early and often:** encourage involvement across all phases of product development.
- **Treat patients as collaborators:** they should be seen and treated as equal stakeholders and not as a target market.
- **Display leadership:** be ambassadors for this cause for the rest of the industry.
- **Be the change you want to see:** proactively provide patient-generated perspectives and evidence to the regulators, payers and market access gatekeepers.
- **Share your lessons learned:** document failures as well as successes.
- **Collaborate to develop best practices:** share tool kits with your peers.

Source: *Value in Health*

"We try to involve the user as early as possible within any development. Typically, we undertake exploratory design research with patients to understand their experiences, attitudes to the condition, therapy and existing product offerings."

Right: John Burke, senior consultant at Team.

This was demonstrated in 2015 with the battle to see which PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) would be first to market: Amgen or Sanofi-Regeneron. Sanofi-Regeneron won with Praluent, which was followed by Amgen's Repatha a few months later.

"Surprisingly, these competing drugs were initially launched in the same device," says Burke. "The opportunity to differentiate these competing therapies through device design or user experience improvements wasn't possible in the race to launch."

The way to success

When it is possible and practical to implement a patient-centric approach, there are a number of best practices to increase the chance of success.

"We try to involve the user as early as possible within any development," explains Burke. "Typically, we undertake exploratory design research with patients to understand their experiences, attitudes to the condition, therapy and existing product offerings."

This sometimes means going above and beyond the call of duty. "We often visit patients in their homes to see first-hand the realities of living with and managing a chronic condition," says Burke. "It's not uncommon to see a fridge dedicated to storage of temperature-sensitive medications or huge boxes containing different medications required to manage a complex condition."

It is also key to continue to ask questions throughout the entire process. "We seek to identify the key 'pain points' or challenges faced by users and turn these into opportunities," adds Burke. "For example, 'How might we simplify the management of this condition' or 'How might we reduce the pain experienced during injections'. This in turn guides the concept generation activities, and informs the key decisions and forward strategies."

What does the data say?

In addition to engaging with patients directly, big data can also provide value throughout the process. This includes vast volumes of information as well as predictive medical analytics. Electronic medical records from hospitals and medical data from social network services can elucidate patient needs and help to improve the efficiency of drug development.

A good example where patient-centricity is working well in practice is

Amgen's Neulasta OnPro device. Following extensive research with patients, Amgen relaunched its market-leading white cell boosting Neulasta in a custom version of the OmniPod device, called OnPro.

"In doing so, they not only raised the bar for biosimilars in development but offered clear benefits to users," explains Burke. "Following a strong dose of chemotherapy, users are able to stay home, rather than visit their doctor the following day to receive the injection."

It is not always easy to implement this approach but it is clearly worth the time and cost investment. With momentum growing within the industry, this will become increasingly common, bringing benefits to industry and patients alike.

"I believe the outlook is positive, we're seeing more and more companies engaging with users early in the development and translating these insights into their marketed products," says Burke. "My hope is that as the launch of innovative patient-centric delivery devices and therapies start to shape the market, other companies will see the value and opportunities offered by engaging users early." ●

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With the advancement of biologics and protein drugs driving rapid growth for the auto-injector industry, **SHL Group**'s in-house automation capabilities enable the company to meet the shifting market demands in terms of quantity and quality.

Initially, SHL's manual and semi-automated manufacturing capabilities adequately fulfilled low to medium-volume device orders that covered just a few therapeutic areas. These capabilities also provided customers with a level of flexibility for clinical or commercial needs. Today, because auto-injectors have become one of the more prevalent solutions for self-treatment of biologics, demands are increasing and suppliers must keep up.

When multiple customer demands require a production output of millions of devices per year, scaling up production is inevitable. In scale-up production, consistent quality that meets the highest regulatory requirements must be addressed. SHL's automated assembly and testing machinery offers the reliability to mass produce products in identical quality from the first assembly unit to the last.

The development of SHL's automation machinery complies with a standardised process that ensures consistency in quality. Processes include the definition phase, the engineering phase, the manufacturing and assembly phase, the debug and final test phase, and the shipping phase.

Considered the most crucial stage, the definition phase demands fully agreed upon machine specifications for a smooth flow in production. Unquestionably, altering an image on a 3D CAD drawing is more feasible than replacing or modifying actual machine parts.

In-house automation: key to an accelerated process

SHL's in-house manufacturing capabilities ensure a parallel development process across numerous departments, meaning seamless integration between design, tooling, moulding and automation phases. Streamlined communication between machine builders and device designers at the early stage of device development ensure that components are applicable for assembly lines.

The advantages of in-house automation also include close collaborative efforts among device design teams, quality teams, manufacturing teams, and risk teams to efficiently identify possible failures and risks prior to the design or manufacturing process, such as failure modes and effects analysis (FMEAs) and process failure mode effects analysis (PFMEAs).

SHL's mechanical and software engineers adhere to systemised procedures and guidelines to determine accuracy and precision in machine development. Machines that are built follow stringent quality management systems to comply with industry regulations. The project management department ensures that projects stay within the specified time frame and budget.

Stringent software validation processes are also implemented to meet industry regulatory standards. Furthermore, in-house service engineers provide on-site maintenance and service for SHL's assembly and test equipment to safeguard continued operations without issues in a 24/7 work environment.

Modular approach: essential to increase flexibility

With the capability to design and manufacture assembly and testing equipment in-house, SHL's automation department offers a wide range of manual, semi-automatic, and fully automatic machine systems to the industry that cover two core capabilities – assembly and testing.

In response to varied market demands, SHL has introduced the modular approach to both assembly and testing equipment, heightening its flexibility in production. The importance of offering a more flexible automation programme beyond high-volume production lies in the propensity of the rapidly changing medical device industry. Drugs under development experience numerous clinical trials, pilot market-testing and user feedback that could well impact the order quantity from a single customer.

In-practice application: assembly and testing

Modular systems in assembly and testing equipment offer repeatable methods that drive down costs, mitigate risks, shorten lead times and increase efficiency. A modular platform supports SHL's 'low-volume/high-mix', multi-device strategy in assembly and testing. By utilising a modularised platform, several different devices in low-volume batches could be assembled on one machine. This strategy drives down costs for new equipment investments and eliminates unwanted idle time for single-use machines. Regarding device-testing equipment, the modular approach drives down possible revalidation processes due to its redundancy system. By altering a few components or equipment parts to accommodate test devices, the modular platform ensures a smoother process in product testing.

Through this, SHL increases its flexibility in outputting low-volume, medium-volume and high-volume orders, while driving down costs and mitigating potential risks. ●

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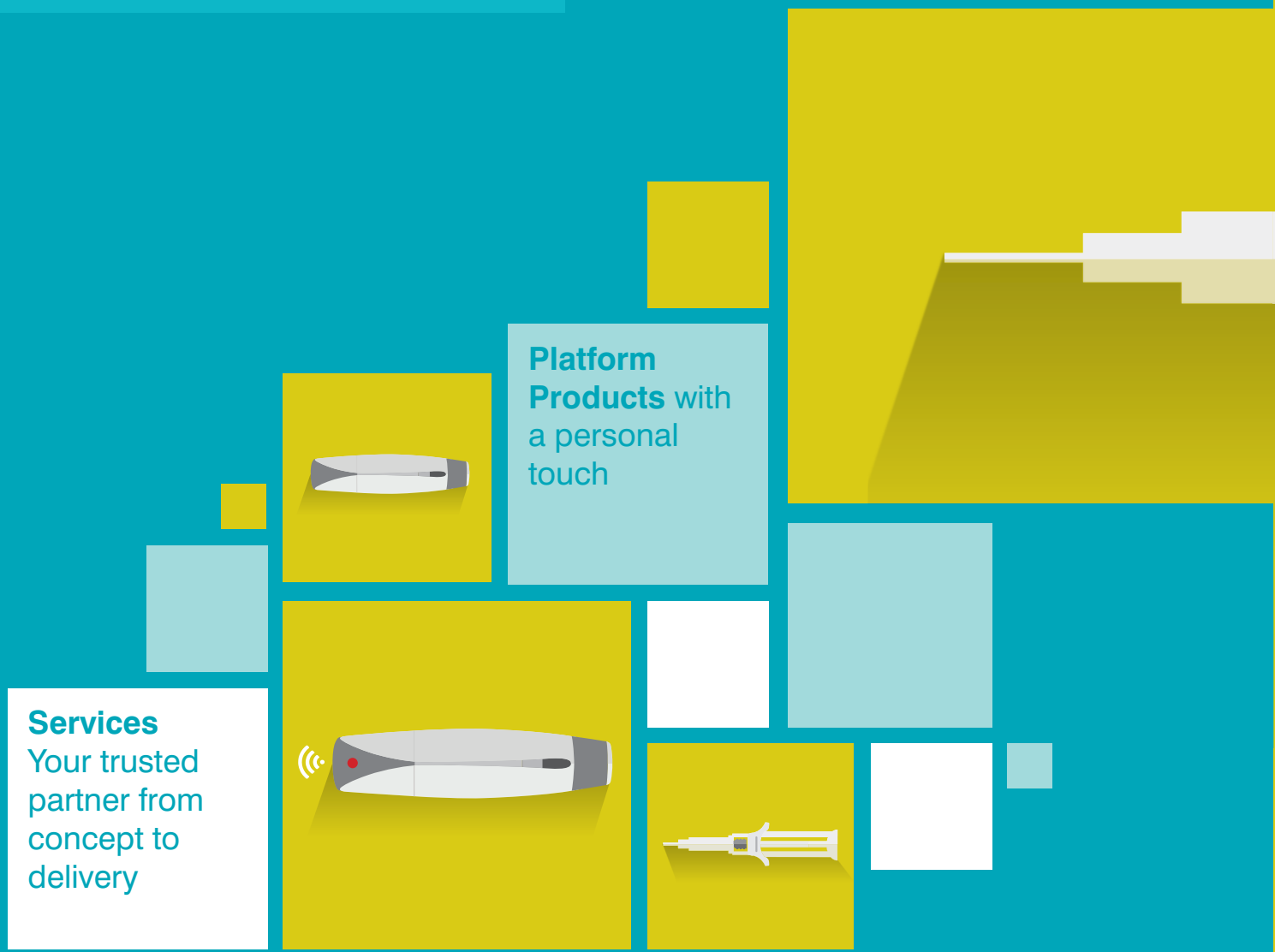

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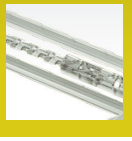

Owen Mumford
Pharmaceutical Services

Freedom of the micro pump

Sensile Medical, a Gerresheimer company, has launched its first micro pump with Ever Pharma offering a new solution to the current quality of life for patient's with Parkinson's disease, and more autonomy for patients with more advanced symptoms of the condition – a full day's treatment, just once a day.

The first micro pump from the Gerresheimer subsidiary Sensile Medical is now available on the market and may give Parkinson's patients more autonomy in their day-to-day lives.

Developed by Sensile Medical, especially for EVER Pharma under the brand name D-mine Pump, this wearable infusion device with a micro pump recently received European CE certification and has already been launched in several European countries. The compact, patient-friendly infusion pump is used for the continuous subcutaneous administration of the drug to treat the advanced stages of Parkinson's disease.

Looking at current treatments available, patients often have to swallow multiple units of drugs while adhering to a strict schedule. Additionally, one or more self-injections of medicine were required. All this compromised their quality of life. In order to ease the control of the disease, a continuous infusion using the pump offers a beneficial option. For most patients, a full day's treatment can be set up just once a day, giving them more autonomy in their daily lives.

Sensile Medical's new wearable micro pump provides more autonomy for patients with Parkinson's disease.

A perfect fit: modular and flexible components

A Parkinson's patient uses this 20ml micro-infusion pump on a daily basis. Sensile's modular and flexible system – providing a multi-use reusable, containing software and electronics as well as a motor, feedback elements and power source together with the single-use disposable that is exchanged with every new drug filling – is the perfect answer for this specific therapy.

Considering the impairments caused by the disease, it was crucial to develop a device that is safe and easy to handle for those having difficulties coordinating their movements. Small, discreet and easy to carry were further goals that were achieved from a device look-and-feel perspective.

Fully patient centric – basal and bolus fit to each patient's needs

It was mandatory to have a built-in automated drug transfer from the vial to the device. A minimal number of buttons and a multicolour screen interface allow for the adjustment of the pump according to every single patient's needs for basal and bolus drug flow, as well as adapting the dose whenever needed. Plain text menus also improve the handling. With Sensile's micro pump technology these features and settings are an integral part of assuring precise and accurate dosing.

The integrated software and electronics, fully adapted to the specific therapy, allow the integration of multiple languages supporting the launch in various countries, giving the patients the freedom to choose their language of choice. To avoid complicated flow rate calculations for this specific treatment, the device flow rate was set to mg/h instead of ml/h for delivery.

Data history can also be looked up, and supports better management options to HCPs and no additional daily paperwork for the patient.

"For most patients, a full day's treatment can be set up just once a day, giving them more autonomy in their daily lives."

Based on its excellent dedicated team, technology and experience, Sensile Medical has delivered an ambitious infusion pump with highly innovative user requirements fully customised to the patient and pharma company's needs. ●

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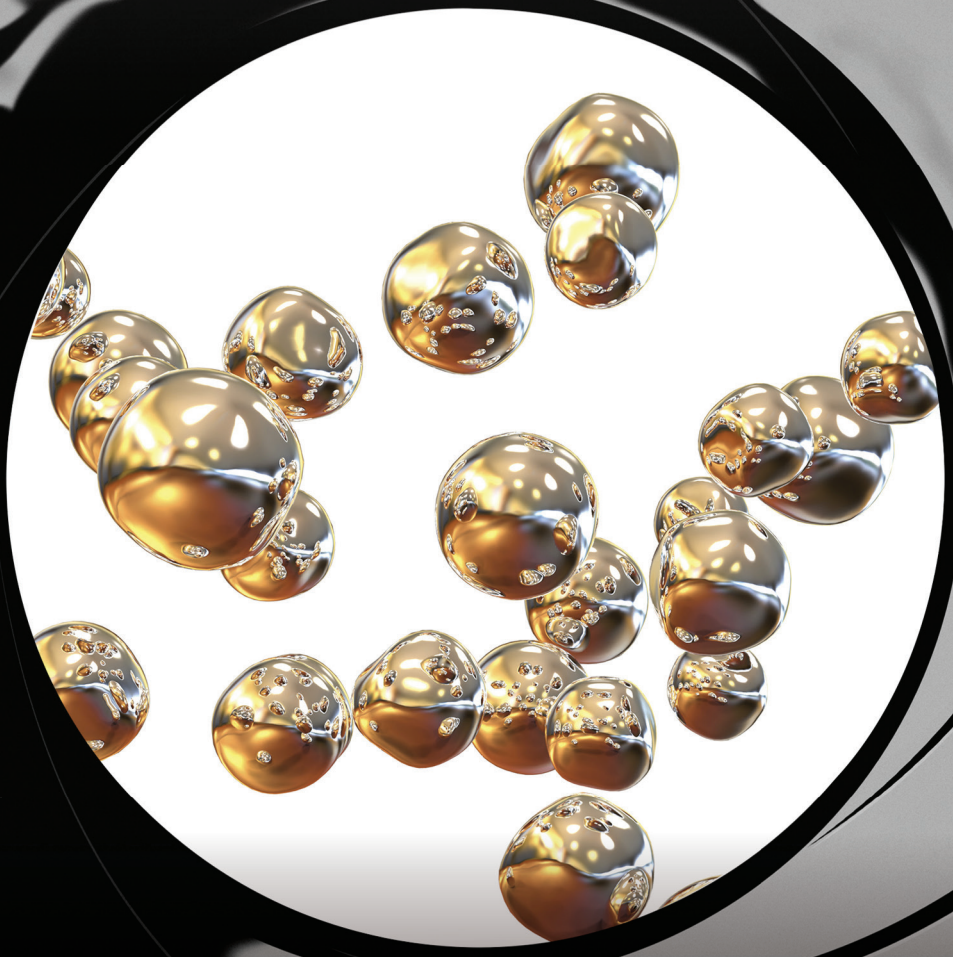


Using gold nanoparticles and an intriguing protein pair called SpyTag and SpyCatcher, researchers at the University of Lincoln have pioneered a new approach for delivering nanomedicine more cheaply and effectively. Isabel Ellis talks to senior lecturer and lead author **Enrico Ferrari** about sneaking medicine through the bloodstream.

It has not quite got the cultural cachet of a nuclear apocalypse, but everyone knows how cyberwarfare goes. A spy with a thumb drive; an unprotected USB; secrets stolen, virus shared: civilisation in ruins. But wait. Stop catastrophising. Let's start again and see if it does not turn out differently. This is a spy story, remember. It's got to have a twist.

The one with the thumb drive used to have a partner. Both were inseparable – practically a single operative, until the meticulous blades and levers of counter-intelligence prised the two apart. Now one holds the virus and the other the antidote. There's no agency more powerful than the one drawing the two back together.

Kateryna Kon, LeStudio/Shutterstock.com

Were the University of Lincoln's Enrico Ferrari a scriptwriter, that might be how the movie would be pitched. For better or worse, Ferrari is a scientist. Rather than screenplays, there are journal articles – and a new drug delivery method for nanomedicine ready for in vivo trials. The spy is *streptococcus pyogenes* (S-PY), a scarcely noticeable extra in most people's throats, but the uncharismatic villain of pharyngitis, impetigo and necrotising fascitis. In 2012, researchers at Oxford University's Department of Biochemistry split the bacterium around its highly unusual extra covalent isopeptide bond to create SpyTag and SpyCatcher, two proteins that spontaneously conjoin when they come into contact.

For some, this could be a love story, but, from Ferrari's perspective, SpyTag and SpyCatcher are microbiology's USB. They form the basis for the plug-and-play model for delivering nanomedicine. At the moment, the use of nanoparticles to precisely target otherwise insoluble or hard to administer treatments like chemotherapy, is an exciting area of scientific research. "But maybe in the sense of drugs on the market," says Ferrari, "it's not enormously successful." The USB standard was developed to make computers easier to use for those with no experience; Ferrari's goal is to do something similar for nanomedicine.

In the 2018 paper 'Modular assembly of proteins on nanoparticles', published in *Nature Communications*, Ferrari and the team showed that SpyCatcher/SpyTag can be used to decorate gold nanoparticles with proteins for more targeted drug delivery. Less summarily, SpyCatcher can be immobilised on gold nanoparticles with the enzyme Glutathione S-Transferase (GST) without losing any functionality, making it possible to covalently bind therapeutic proteins modified with SpyTag. "With SpyCatcher-SpyTag, you have a sort of automatic connector of proteins that works by simple mixing and forms a very solid bond," enthuses Ferrari. "Anything that expresses SpyTag will bond to SpyCatcher, so, if SpyCatcher is already fused to GST, it means that will inevitably bring it to bind with gold. It's the USB socket and plug that I was missing."

This approach has a host of advantages for the gold nanoparticles that Ferrari has worked on so far, but the most exciting element is its potential to be cheaply and universally applicable for different combinations of proteins and nanomaterials, just as the original USB was for computers and peripherals.

"You have particles of different materials," Ferrari goes on to explain. "Then you have a variety of biomolecules that scientists are trying to conjugate to nanoparticles to make them active or to make them specific for some target."

This requires an enormous effort of optimisation to do that for every combination. "But if you are able to make a particle that will hold this USB socket, you don't need that effort," says Ferrari. "You just need to make a different adapter in place of GST, which instead of binding to gold will bind to iron oxide, for example. As long as your molecule has the USB plug, it will work."

Make the drop

Imagine one loose brick, one cut-out book, one hollow coin in a city of millions. It is used for a dead drop – a decidedly pre-cyber way for spies to exchange or transmit information without meeting. Still, it would be a key plot point for Ferrari's USB thriller. Armed only with some vague clues about its possible whereabouts and the knowledge that it is likely to be near to some chalk hieroglyphs (which were often used to indicate that a drop had been made), one operative is tasked with finding it.

That is the best espionage-based analogy for the task of delivering nanomedicine to the right place in the body. The proteins on nanocarriers need to trigger binding events with very specific target cells so they can be absorbed by endocytosis. As such, therapeutic proteins are typically chosen and engineered for their affinity with a specific receptor on target cells.

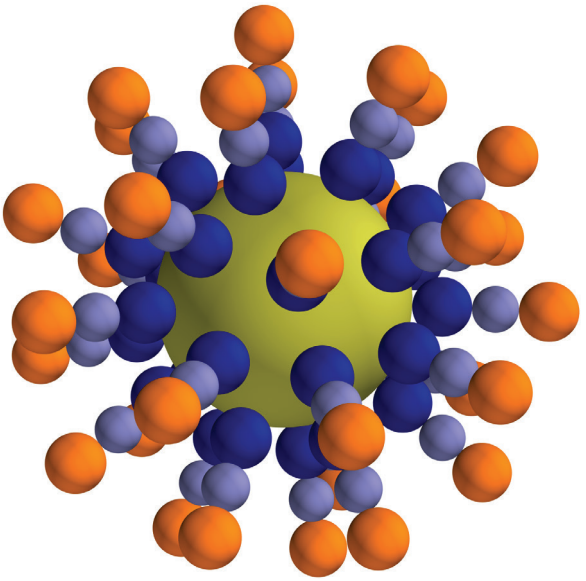
However, what Ferrari euphemistically calls "the recognition event", becomes much less likely if those proteins are damaged as they travel through the body. While an operative could do with some clear directions, the medicine needs what Ferrari refers to as "a clean and well-organised assembly" to ensure the interaction between the targeting protein and its target.

Just as the best spies can become double agents if they are not properly monitored and handled, the most promising nanocarriers can 'leak' if they are poorly assembled. To maintain an equilibrium in the bloodstream, blood serum proteins work to cover up

1–100nm

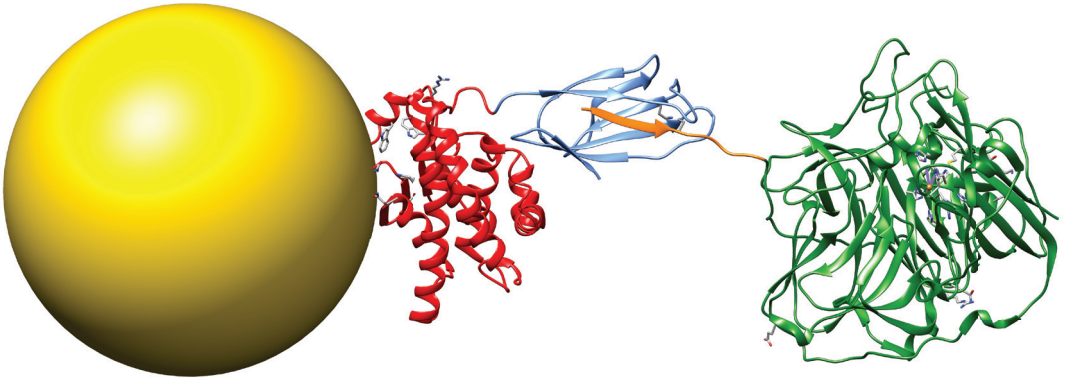
Size of a nanomaterial.

Journal of Pharmaceutical Investigation



Representation of a nanoparticle decorated with modularly assembled proteins.

Enrico Ferrari



Components involved in the nanomedicine drug delivery method: red is GST, blue is SpyCatcher and green is a hypothetical enzyme.

Enrico Ferrari

or detach therapeutic molecules from nanoparticles in vivo, creating a 'corona' that can impact the medicine's chemical make-up and disrupt its therapeutic effect. Once contact is made, those proteins also activate the body's immune system, which will attack the nanocarrier as a potentially dangerous invader. All in all, it is exceedingly difficult to predict how this might play out in different individuals.

"That's the problem," says Ferrari. "It might be that the proteins that stick to the particles will overwhelm the chemistry that you originally developed on the surface, so it won't do exactly what you intended. Even more dramatically, you might end up having particles that work well on your bench but have completely different effects in vivo, because the corona forms differently."

But spies know how to avoid unwanted attention. These spies in particular comprise one of the very few systems for constructing complete multi-protein mega-molecules without chemical cross-linking. With GST, the pair covalently immobilise therapeutic biomolecules on gold nanoparticles, locking their chemical structure into a functional, hierarchical corona with its own equilibrium, thus preventing the dynamic exchange of molecules in the bloodstream. Whereas current approaches cross link particles to proteins without controlling the strength of their connection, Ferrari's method allows for the best orientation of covalent bonds on both the gold-side and on the protein-side, guaranteeing that there will be no leaks.

"It is a hybrid method between chemical conjugation and passive adsorption," Ferrari explains. "It has all the advantages of passive adsorption, which is simple mixing – easy to handle – but it also has the advantage that it provides covalent bonds between all the individual components in a layer-by-layer deposition."

Leaks are hard to explain, but it is far from the only problem with the current nanomedical paradigm. At present, all the different materials, molecules and mixtures that constitute targeted nanomedicines need to be approved by regulators. As Ferrari fears, "Having an enormous number of combinations of elements, that you have to make use of to make a variety of different nanomedicines with different proteins, might be unsustainable, too expensive or too difficult to do."

However, with a modular platform, the same building blocks can be established as safe to reuse with different molecules and nanocarriers. "It's a mix-and-match procedure that may save on getting nanomedicine through regulatory bodies," explains Ferrari, who is well aware that it is just as important as human ones.

The remarkable discovery

None of this emphasis on tiny spycraft is to underplay the importance of GST. Ferrari credits its remarkable, previously undiscovered ability to form sulphur bonds to gold and silver as making the difference in the team's research.

Still, to fully leverage the potential of modular nanomedicine, Ferrari needs to find appropriately strong equivalents to GST for other clinically significant nanocarriers, such as silica and polymers. The challenge comes from the fact that those materials are far less reactive than gold or silver, which makes it highly unlikely that the interaction can be built around a similar covalent bond.

While alternatives are investigated, Ferrari is looking for the right pharmaceutical partner and therapeutic molecule to use with gold nanoparticles for in vivo tests and, ultimately, a full clinical trial.

That said, once Ferrari finds a way to attach the USB to materials other than precious metals, it is believed that the approach could achieve even greater universality as a conjugation method for nanoscale environmental biotechnology. The example of safely delivering a particular enzyme to contaminated soil without compromising its functionality is given: "The same way nanoparticles are used for drug delivery, passing from the syringe to the target in the human body, I think they can go from a bucket to the soil to target contaminants," Ferrari explains.

The main difference? "If you're going to deliver a drug into a patient maybe you can use gold, but if you have to spread it across a contaminated field – that's probably a bit expensive." After all the blood, the gold, the intrigue and the paranoia, who could begrudge two spies their rural retirement? ●

Customised phyto-pharmaceuticals

Anklam Extrakt offers ready-to-market finished product concepts.

Anklam Extrakt stands for the top expertise in the development, production and research of high-quality plant extracts. Those extracts – made from either leaves, flowers, roots, berries, and other parts of the plant – are produced solely in accordance with the requirements of GMP and HACCP quality standards.

The company is situated in Germany and produces each and every extract in its own production site in the Hanseatic town of Anklam. As an up-and-coming company, Anklam Extrakt is committed to advancement, just as much as it is to sustainability. Therefore, the company has a strong focus on modern processes, state-of-the-art production facilities and the expertise of experienced employees with an emphasis on providing an overarching service for its customers.

One of the unique features of Anklam Extrakt is the designing and the planning of customer projects. The technical development is conducted and the entire documentation is issued for each customised extract. The regulatory affairs department accompanies the extract development from the start of the project to the registration and beyond.

To provide an even bigger benefit to its customers, Anklam Extrakt has created a project named phyto2market. With strong partners, Anklam Extrakt is not only able to provide high-quality plant extracts, but also support its customers in bringing herbal medicinal finished products into the market with a professional and complete service concept. From the sourcing of the raw material, the extract development, the finished dosage form and, finally, the dossier with the complete management of the marketing authorisation process, Anklam Extrakt, together with its partners, take on the professional project management. This results in tailor-made concepts with fast market access and high success probability for the customers.

Further information
Anklam Extrakt
www.anklam-extrakt.com

Pioneering partner for peptides

Bachem is the leading independent supplier of peptidic active pharmaceutical ingredients (APIs) for the human and veterinary pharmaceutical market. Since the company's foundation in 1971, Bachem's concepts and technologies pioneered industrial peptide manufacturing. The company's pioneering mindset drives it to continue developing innovations and offering all integrated services needed to bring its partners' breakthroughs to the market.

A strong partnership is the key to coming up with innovative concepts and molecules to introduce into clinical development. Bachem's custom-made peptide service supports lead-finding and optimisation during preclinical development. The company's partners can trust in its support and guidance from early development and selection of the lead compound, throughout all the clinical phases and the final drug approval. Each production step is scrutinised in order to guarantee manufacturing reproducibility and scale-up possibilities. Process validation and control is the result of the intense partnership between Bachem and its customers.

Bachem has the capacity to produce peptide APIs from Gram scale up to hundreds of kilograms.

As a leading peptide contract manufacturing organisation, Bachem guarantees the reliable supply of the drug substance by coordinating its activities closely with its partners. The company is currently involved in more than 150 cGMP development projects targeting new chemical entities (NCEs) and offers a range of more than 30 generic drug substances. Bachem has the capacity to produce peptide APIs from Gram scale up to annual quantities of hundreds of kilograms. The FDA and local authorities regularly inspect the company's GMP facilities, which are located in Switzerland and the US.

In addition to its close to 50 years of experience in the manufacturing of drug substances, Bachem also has a strong regulatory background. The company is well prepared to fully support its customers with the required regulatory documentation such as drug master files (DMFs).

Headquartered in Switzerland, with subsidiaries in Europe, the US and Asia, the Bachem group has a global reach and shows total commitment to quality, innovation and partnership.

Further information
Bachem
www.bachem.com

High grade hits the market

CBDepot introduced the world's first GMP natural CBD isolate to the API segment.

CBDepot's work has been constantly driven by innovation. The company has been bringing new isolated cannabinoids, and new preparations for food and food supplement sectors, which tackle the Novel Food regulation on hemp derivatives in the EU.

CBDepot has already introduced the world's first pharmaceutical GMP natural CBD isolate to the API segment. This product was debuted during the biggest pharmaceutical event in the world, the CPhI in Frankfurt, Germany, through CBDepot's contract manufacturing partner, Vakos XT.

CBDepot, in cooperation with its distribution partner Farmakem, won a tender for deliveries of GMP CBD to a public paediatric hospital in Ljubljana, Slovenia, for the co-treatment of child epilepsy.

Farmakem played a vital role in applying the regulatory development of the product, as well as in the process of public tender. This is a major breakthrough in cannabinoid-based therapies in the EU and could not have happened without the dedication of Farmakem and Dr Neubauer.

Dr Neubauer has a long record of clinical experience in treating his paediatric patients using CBD in the treatment method, and reports that the best outcome is when CBD of natural origin is administered. In 2019, again through Farmakem, this active substance was confirmed as the substance of choice at the paediatric hospital in Ljubljana and additionally also in the tender at the Institute of Oncology in Ljubljana.

Further information
CBDepot
www.cbdepot.eu

Join the celebration

CPhI Worldwide, organised by Informa Markets, recently announced that the CPhI Pharma Awards, powered by Informa Pharma Intelligence, will be held on Tuesday 5 November 2019 in Frankfurt, Germany. The ceremony for this year's awards, which celebrates innovation in the pharma and biotech industries, will take place on the first evening of the world's largest pharmaceutical exhibition, CPhI Worldwide.

Tara Dougal, head of content for CPhI, states, "It is always exciting to launch the CPhI Pharma Awards, especially when there is always so much going on within the industry. The quality of last year's entries was exceptional and it was a pleasure to be able to meet so many entrants and nominees at the Awards Ceremony."

The CPhI Pharma Awards celebrates the innovation within the pharma and biotech industries.

Since 2004, the Awards have brought together leaders from across the pharma and biotech industries to celebrate the thinkers and creators who are breaking new ground, with a strong emphasis on promoting companies committed to driving the industry forward.

Winners will be revealed live at the CPhI Pharma Awards Ceremony, which will provide an evening of celebration that brings together pharma executives to toast industry excellence as well as enjoying the company of friends and peers. For many of the event's attendees, it is the perfect occasion to extend their hospitality to their clients and associates during the world's largest Pharma exhibition, CPhI Worldwide.

While attending the gala, visitors can:

- network with international decision-makers from leading companies in an informal setting
- be recognised as one of the top companies supporting the industry and recognising those making a difference to the industry
- share in the excitement when the winners are announced.

Further information
CPhI Worldwide
www.cphi.com/awards

The next level for soft chewing tablets

Calcium Carbonate as DC granules with gum arabic is a newly developed product created by the company Dr Paul Lohmann, named Calcium Carbonate DC 97GA. The product is designed for direct compression into soft chewing tablets and chewing gums combined with a neutral taste and a pleasant mouthfeel. Alongside maltodextrin, corn starch and PVP as binding agents, gum arabic is a perfect addition to the Dr Paul Lohmann's DC granules product line. In contrast to PVP, gum arabic is permitted for use worldwide as an additive, allowing for a global product launch of the finished product.

Calcium Carbonate DC 97GA is dust-free and free-flowing, the product is not only permitted for food and food supplements, but it can also be used in pharmaceutical applications as excipients. Furthermore, due to the high calcium content of the product, the tablet size can also be reduced. Dr Paul Lohmann performed tableting tests in their in-house application lab and demonstrated the differences in tablet height and hardness between well-known binders such as PVP, maltodextrin and corn starch. Depending on the customer's desired dosage form and target size, Calcium Carbonate DC 97GA could be the medium of choice.


Calcium Carbonate DC 97GA is designed for soft chewing tablets and chewing gums.

Advantages of the product at a glance include:

- pleasant mouthfeel
- neutral taste
- dust-free
- free-flowing
- permitted for food and food supplements
- reduced tablet size due to the high calcium content.

Further information
Dr Paul Lohmann
www.lohmann4minerals.com

Electronic devices to improve patient adherence

Nemera designs, develops and manufactures devices that truly improve patients' lives for nasal, buccal, auricular, inhalation, dermal and transdermal, parenteral and ophthalmic delivery.

Nemera produces and provides millions of multidose eye droppers for preservative-free formulations. With an ageing population and an increasing number of patients suffering from chronic eye conditions that require regular topical treatment, it is increasingly necessary to improve the effectiveness of drug delivery as well as the patient adherence.

There are several factors that can attribute to low adherence rate, such as a lack of knowledge about the importance of following a

Nemera's e-Novelia has been conceived to make patients' lives easier.

strict treatment schedule by the patient, uncomfortable side effects of the medication as well as difficulty in administering the treatment. This is why Nemera developed e-Novelia, a new electronic add-on technology, offering additional features to Nemera's preservative free eye-dropper Novelia than any standard eye droppers that already exist on the market. e-Novelia has been conceived to make patients' lives easier, by offering a method that provides an increased comfort and usability to their treatments.

Digital enhancement can assist with drug delivery through aiding the patient with administration as well as giving them reminders about when their next dose is due. Using smart add-on technology, patients can also benefit from digitalised and interactive instructions via their mobile device. Patient awareness can be increased with reminders of when to take a dose or when to replace their medication.

This breakthrough technology is a concrete innovation that brings benefits not only to patients, but also to all stakeholders involved. This includes healthcare practitioners as well as pharmaceutical companies.

Nemera's innovative devices will appear at several promising events, including CPhI Worldwide in Frankfurt on 5–7 November.

Further information

Nemera

www.nemera.net

NIR based PAT solutions

Founded in 1993, Sentronic has over 25 years of experience in delivering innovative spectroscopic solutions. The company is a recognised leader

SentroPAT FO is a compact, ruggedised system for monitoring unit operations in processing solid dose pharmaceuticals

in developing PAT solutions, and delivering all aspects required for the successful implementation of PAT in pharmaceutical solid oral dose development and manufacturing. As innovator and partner, Sentronic helped users in realising online measurements using the SentroPAT NIR systems as part of the FDA PAT initiative, as early as 2003. These technology platforms and photonic solutions established the basis for Sentronic's robust, turn key products based on near infrared spectroscopy.

By utilising the Sentronic NIR diffuse reflectance PAT solutions, typical unit operations in batch and continuous processing can be monitored in real time. Based on the powerful SentroPAT system series, Sentronic offers solutions to realise PAT in all project phases, from early process and product development, to process transfer to routine operation, as well as aid process troubleshooting. SentroPAT systems have more recently been deployed with success in continuous manufacturing (CM) process implementations at several different innovator pharmaceutical companies worldwide and across several CM technology platforms.

All Sentronic systems comply with US, European and Japanese pharmacopoeias monographs for NIR spectrophotometer performance. All systems also comply with pharmaceutical industry requirements and regulations, and the system and software are developed according to GAMP under comprehensive quality management system. Full life cycle documentation and validation packages, as well as services for GMP qualification, complete the portfolio Sentronic is offering to customers in the pharmaceutical industry.

Working with an established and global partner network of experts, Sentronic provides comprehensive services and close support to the customers.

Further information

Sentronic

www.sentronic.eu

Opportunities for implementing metathesis catalysts

XiMo was established in 2010 with the vision of commercialising certain ruthenium, molybdenum and tungsten metathesis catalysts, with exclusive titles to all material intellectual property. XiMo is continuously developing its production scale, as well as its new catalysts and technologies.

Improvements in the field of olefin metathesis over the past two decades opened an ever-increasing number of opportunities for the pharmaceutical industry to implement and use metathesis catalysts, amongst others, for some potential anti-cancer drugs and many biologically active natural macrocycles that contain cis carbon-carbon double bond. As economically feasible synthesis is key for drug discovery, development and scaled production, XiMo offers both families of ruthenium and molybdenum/tungsten metathesis catalysts that are highly Z-selective, simplifying the production of those molecules and making their production more cost-efficient. In general, the activity of metathesis catalysts allows their use in very small amounts, in many cases below 0.01 mol%, relative to the substrate, making these processes economically and environmentally attractive. For example, Nakadomarin A can be prepared from its dialkenyl precursor by ring closing metathesis reaction with high Z-selectivity (94%) and good yield (63%). This demonstrates only one example of the broad application potentials of XiMo's metathesis catalysts.

XiMo is continuously developing production scale, and new catalysts and technologies.

XiMo possesses close to 900 catalysts; several are Z-selective, both in the ruthenium or molybdenum/tungsten-based catalyst families, technology and expertise to produce metathesis catalysts at several kilograms scale outside of a glovebox.

In close collaboration with its clients' R&D and production, XiMo maps its clients' needs, the circumstances of the facility's capabilities and limitations, and offers solutions to reach the best results by reducing production cost

Contact the company to find out how its metathesis catalysts and technology offering can simplify syntheses.

Further information

XiMo

www.ximo-inc.com

4Advice 27
www.4advice.eu

Air Canada Cargo 16
www.aircanadacargo.com

AJA Pharma 40
www.ajapharma.com

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www.lohmann4minerals.com

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LTS ..... IBC
www.ltslohmann.de

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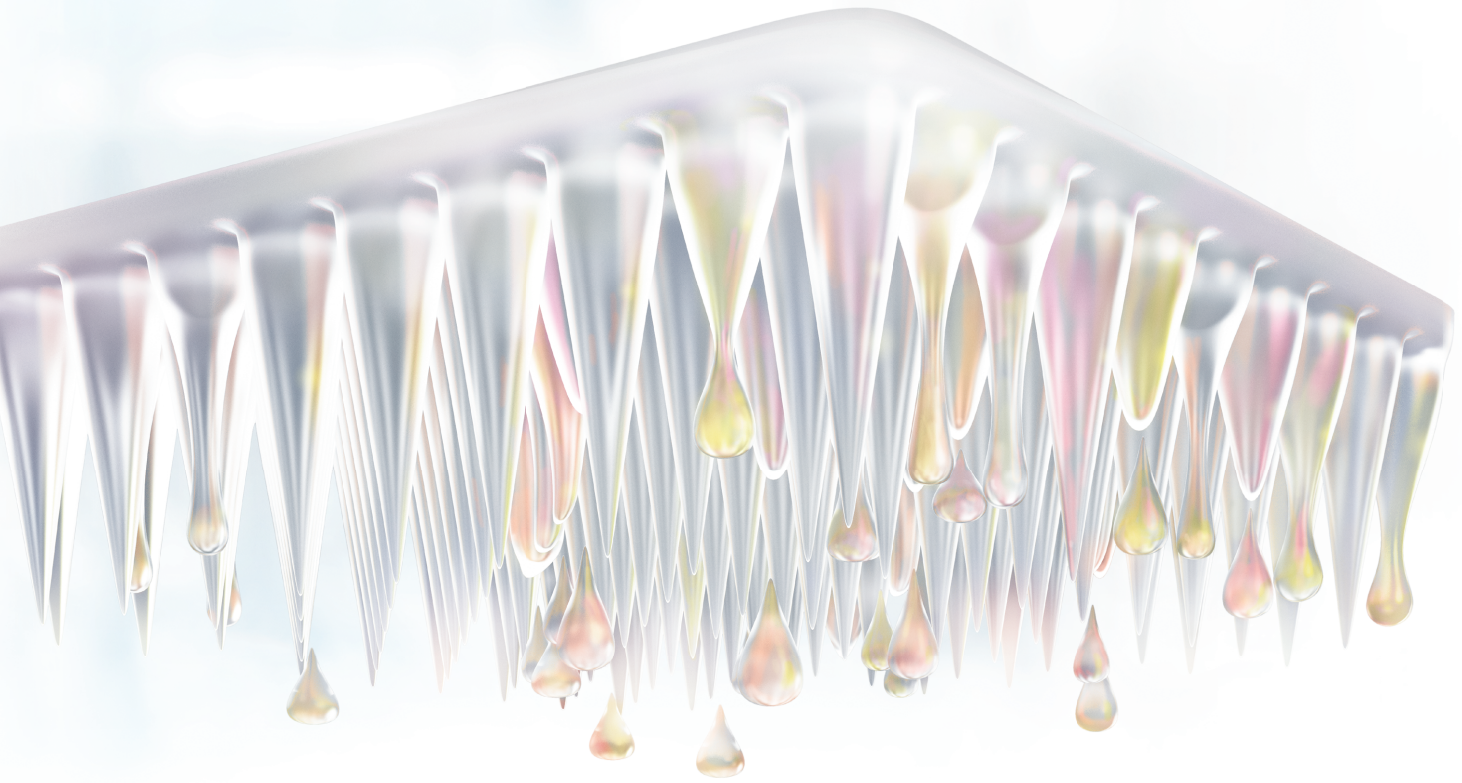

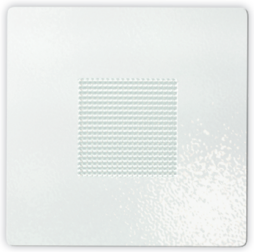

Micro Array Patches penetrate the skin with drug containing microscopic structures, which then dissolve and release their APIs.

We create therapy alternatives for everyones benefit. Please contact us: www.ltslohmann.de

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