WorldPharma

World Pharmaceutical Frontiers

www.worldpharmaceuticals.net

£31.00 €49.00 $65.00 2019 Vol. 1

The missing link

Is blockchain the key to a secure supply chain?

Special supplement:

Supply chain & logistics

Published in association with:

LogiPharma

GlobalData.

EMBALL'ISO

MAKE YOUR COLD CHAIN EFFECTIVE

TLX CARGO

BY EMBALL'ISO

Sharing our expertise

FOR YOUR BENEFIT

- Available **worldwide**
- **Innovative, breathable, performant** and **eco-friendly** solutions
- **Complementary** range

PCM AS A FIBER

REFLECTIVE

RECYCLABLE

WWW.EMBALLISO.COM

On the web...

Keep up with the latest developments across the industry by visiting **www.worldpharmaceuticals.net**

World Pharmaceutical Frontiers
2019 Vol. 1

World Pharmaceutical Frontiers is published by Compelo.

Registered in England No. 09901510.

John Carpenter House,
John Carpenter Street London, EC4Y 0AN, UK
Tel: +44 207 936 6400
www.compelo.com
www.worldpharmaceuticals.net

ISSN 1742-3791 © 2019 Compelo.

SUBSCRIPTIONS

Single issue price:	UK £31	EU €49	US $65	RoW $65
One year:	UK £48	EU €76	US $99	RoW $100
Two year:	UK £77	EU €120	US $158	RoW $159

Subscription hotline: +44 845 155 1845 (local rate)
Subscription fax: +44 20 8269 7877
Email: cs@compelo.com
World Pharmaceutical Frontiers Subscriptions, Compelo, Riverbridge House, Ground Floor, South Tower, Anchor Boulevard. Crossways, Kent DA2 6SL

Printed by Stephens & George Print Group

A brand-new way of working

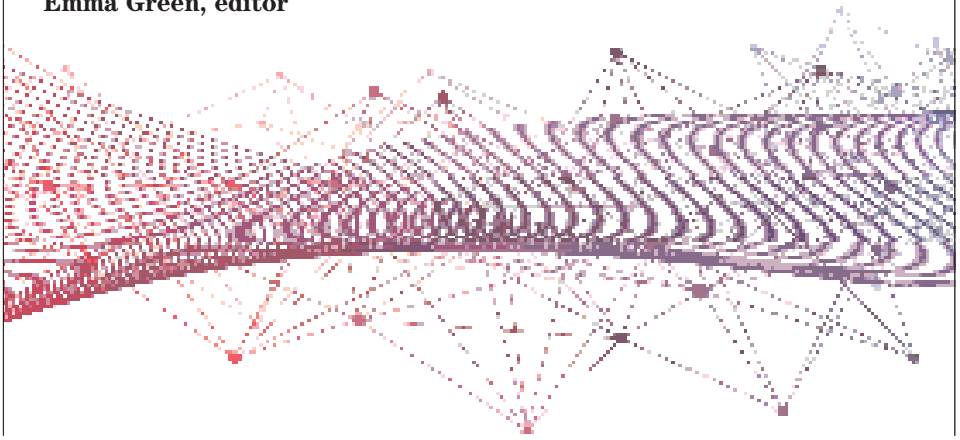
With increasing talk of industry 4.0, there's no doubt that recent technological advancements offer huge benefits to the pharmaceutical industry: enhancing efficiencies, improving precision and providing a more secure supply chain. Although concerns about AI, automation and robotics replacing jobs remain prevalent, these also provide new opportunities for collaboration, empowering both individuals and organisations to work together to drive progress forward. Despite the appetite to integrate these technologies into the supply chain, this is by no means straightforward. The complex and ever-changing regulatory landscape demands a strategic and agile approach.

Nowhere is this more important than with blockchain, as highlighted by Pasi Kemppainen from Santen Pharmaceutical in this edition. Invented in 2008 by a programmer working under the pseudonym Satoshi Nakamoto, this distributed ledger technology remained largely within small hidden pockets of individuals before its recent leap into the mainstream. Its transparent nature provides both big advantages and risks for the industry, and trust becomes paramount.

Although some of these developments bring new issues to the fore, others offer novel solutions to ongoing, unresolved concerns. Track and trace, for example, addresses the huge problem of counterfeiting. Such technologies require substantial investment but these are far outweighed by the costs of inaction as GS1's Geraldine Lissalde-Bonnet and Centrient Pharmaceuticals' Robert-Jan van der Horst discuss in this issue.

It's important to remember that although these advancements are exciting for the industry, none of them wave a magic wand. Their capabilities are certainly impressive but they do need to be utilised mindfully, as highlighted by Karen Taylor from Deloitte in her insights on the use of IoT within the supply chain. Notably, the majority of the limitations surrounding them relate to the way in which they are used, rather than being an inherent problem with the technologies themselves. They provide a wealth of data, but turning these into actionable insights is still a work in progress. This is why discussion, networking and cooperation are more essential than ever.

Emma Green, editor



TEMPERATURE MONITORING OF PHARMA PRODUCTS DURING TRANSPORT

Loading/Packing

- Loggers, preprogrammed with all the stability info are integrated with products
- Logger's ID is paired with ID of the product/shipment
- Easy integration with serialization, tracking and quality platforms
- Possibility to add logistics and product info

Trans-shipment/Import

- Logistic agents can check parameters via NFC without opening the box/pallet
- Current temperature/geolocalisation info is sent to the client, allowing proactivity

Delivery

- PDF report is generated automatically upon reading of data
- All the data is uploaded to the cloud
- The sender gets an automatic proof of delivery

High precision with calibration certificates

Serialization - pairing of the ID's

Compatible with GDP, WHO and EN12830 norms

Compatible with all transport modes

GET IT ON Google Play

Download on the App Store

Compatible with Android and iOS devices

Local and global access to data

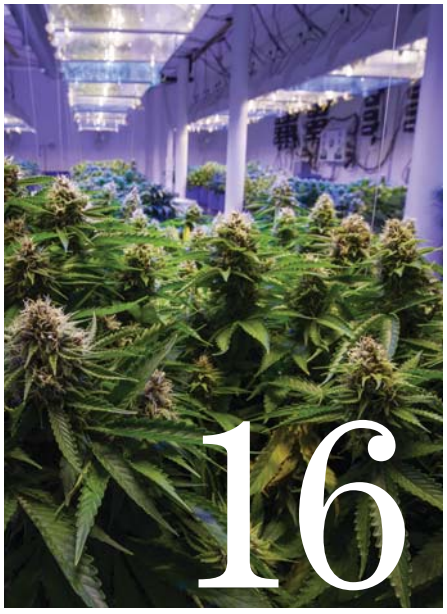
blulog

In this issue

46

Cover story

8



16

Drug delivery

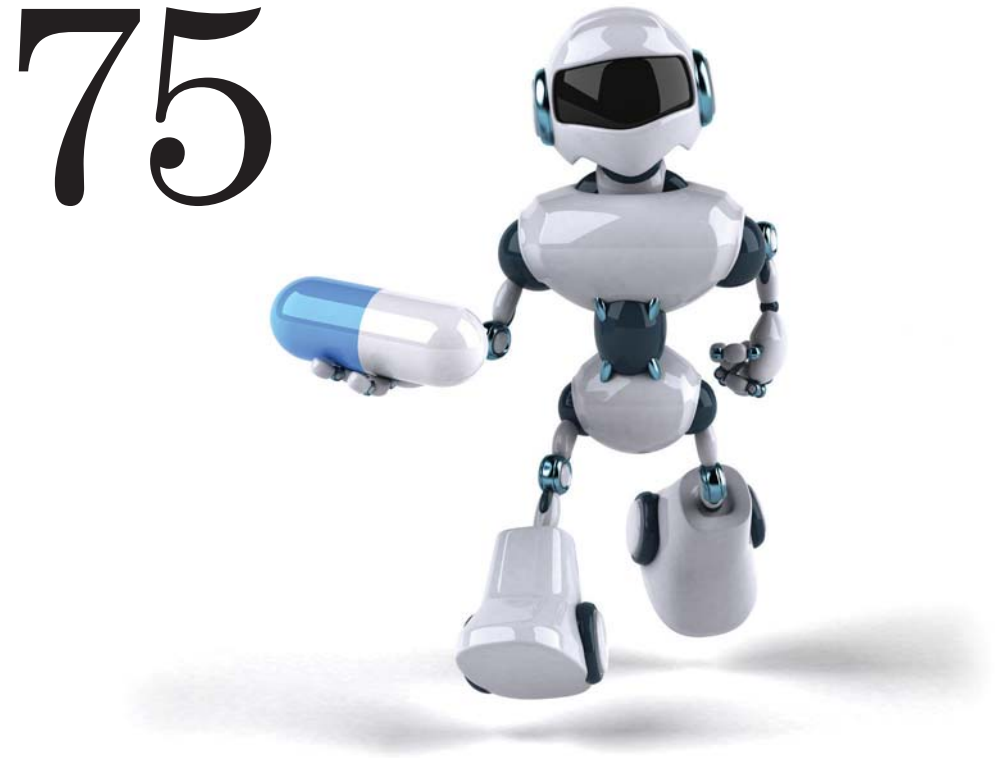
Special supplement

Turn to page 39 to read the Supply chain & logistics supplement.

Contract manufacturing

Manufacturing

Packaging



Spectroscopic Solutions for the Validated Pharmaceutical Industry

Today´s regulated pharmaceutical laboratories must comply with extensive regulatory requirements. Bruker offers together with its high-end FTIR, FT-NIR and Raman spectrometer line comprehensive system validation tools to achieve systematic and cost-effective compliance.

BRAVO Handheld Raman Spectrometer

BRAVO mitigates fluorescence (SSE™), addresses a large spectral range (Duo LASER™) including CH stretching region and is a class 1M Laser product. The intuitive and guide workflow gives the ability for Raman spectroscopy into everybody's hands.

MPA II The New Multi Purpose Analyzer

The MPA II is a powerful tool for developing sophisticated calibration methods for your laboratory or process needs, yet an easy to use QA/QC instrument for routine work.
With its modular technology, it can be configured individually for each analytical task.

MultiRAM Stand Alone FT-Raman Spectrometer

The MultiRAM is a stand-alone high performance FT-Raman spectrometer (1064nm, 785nm additional option). Its large sample compartment allows for utilization of an extensive range of pre-aligned accessories (e.g. for high throughput) being designed to accommodate all sample formats, from powders to liquids in vials.

MATRIX-F FT-NIR Online Spectrometer

Direct measurement in reactors, pipelines and over conveyor belts, leading to a better understanding and control of the process. Its innovative technology provides consistent high quality results with less downtime.

Contact us for more details www.bruker.com/optics

"The most common barriers are at the interface of biology and technology."

Steve Arlington, president of the Pistoia Alliance

Novartis forges new AI alliance

Novartis has entered into a five-year collaboration with Oxford University to apply AI in the prediction of how patients respond to drugs for inflammatory diseases. The programme with Oxford's Big Data Institute (BDI) seeks to tap into anonymised data from around five million patients from the UK and international partner organisations as well as Novartis's in-house data sets in order to improve drug development.

Novartis has been one of the pioneers in the application of digital technologies to healthcare, and already has a number of AI initiatives in the pipeline, including a two-year-old project applying AI to real-world data to better predict breast cancer outcomes.

Both AI and machine learning will be used to find and analyse patterns in the data, using imaging, genomics, clinical and biological information, a feat that would not be possible by humans alone.

The company hopes to gain insights into the characteristics of diseases, such as MS and psoriasis, and identify crossovers between diseases that could help guide the development of new drugs.

MethodDB has been launched

The Pistoia Alliance, a global non-profit that works to lower barriers to innovation in life sciences R&D, recently released proof of concept (PoC) software to enable the digitisation of analytical method descriptions, as part of its method database (MethodDB) project. Greater digitisation will support the use of AI and deep learning by centralising and standardising experiment descriptions against a common ontology, increasing data integrity and scientific reproducibility.

The Pistoia Alliance collaborated with Allotrope Foundation, using the Allotrope Framework technology stack. The MethodDB project is one of the first developments of the lab of the future (LoTF) and will enable scientists to save considerable amounts of time and money when reproducing experiments on different instruments.

"This project is an excellent example of pre-competitive consortia working together to pool resources and expertise," said Dr Steve Arlington, president of The Pistoia Alliance. "By working together we can help to improve the outcomes of experiments and develop life-saving therapies."

FDA funding jumps after US Congress voted to avert shutdown

The US Congress recently approved a deal to avert another government shutdown. The deal includes the biggest increase in FDA funding in several years. President Donald Trump agreed to sign the deal, despite it featuring far less money for the border wall than he wanted. This occurred one day before the cessation of a temporary funding agreement would have triggered another government shutdown. Once Trump backed the bill, the House and Senate subsequently voted in favour of it by large majorities.The bill includes $3 billion in discretionary funding for the FDA, around $100 million less than was requested in the president's budget. However, it still represents a $269 million, which is a 9%, increase over 2018.

The FDA's Centre for Drug Evaluation and Research (CDER) fared significantly better than other parts of the agency. When the FDA submitted its budget request for 2018, it listed the annualised budget for CDER, excluding user fees and field work, at $353 million. This year, CDER is set to receive $525 million, an increase of almost 50%, despite Congress approving slightly less funding than requested.

While the overall increase in CDER funding is huge, Congress and the FDA have different ideas about how the money should be used. Congress has approved $43 million for a "new platform for drug development". This is lower than the $58 million requested by the FDA for this purpose.

$10 million

Amount requested to tackle opioid crisis.

FDA

Pharma's R&D productivity sinks

Despite 2018 being another strong year for the pharma and biotech sectors, including what looks set to be a record-breaking number of FDA approvals, R&D productivity remains a cause for concern.

At the end of last year, Deloitte released their annual update on productivity, and the figures are not encouraging: projected returns on investment in research and development for the top 12 pharmaceutical companies have fallen to 1.9% – the lowest level since the company began its reports nine years ago.

The research by Deloitte's Centre for Health Solutions found that returns had declined 1.8% from 3.7% in 2017. Overall, returns are down by 8.2% since 2010.

The cause of these declines has been the increase in cost to develop and gain marketing approval for new drugs. The average cost is now at $2.18 billion, almost double the cost back in 2010 of $1.18 billion. In addition to these issues, the returns from these assets once they reach the market has also declined. Forecast peak sales per product have almost halved in eight years, down from $816 million in 2010 to $407 million in 2018. Deloitte has made it clear that the industry needs to tackle the problem with new ways of working and greater efforts placed on finding the right talent.

The sector is investing substantially in technologies such as AI, robotics and automation but the results from these innovations will not be realised for the next few years.

$2.18 billion

Average cost of drug development.

Deloitte

Patient connectivity

Five key dimensions of patient centricity

- ✔ **Inclusiveness**
- ✔ **Working in partnership**
- ✔ **Working in a way that shows respect, compassion and openness**
- ✔ **Empowering patients to take control of their own health**
- ✔ **Sharing goals that are patient and family-centred**

Smartphone use

	UK	US	Worldwide
Population	81%	77%	44%

Patients

65% Manage conditions using a smartphone.

70% Use at least one app to manage their condition.

50% Use apps regularly or occasionally.

Patient centricity applications

1 Mobile apps

2 Internet portals

3 Wearables

5.6 million Pharma downloads out of 3.2 billion generated overall by mHealth apps in 2016.

305 to 998 Number of apps produced by pharma companies more than tripled in 2016.

30% Patients surveyed are willing to share data with pharma companies.

75% Industry experts that identified a lack of digital talent as the main challenge.

Source: 'Pharma and the connected patient: How digital technology is enabling patient centricity', Deloitte Centre for Health Solutions.

Small actions with deep impacts

Supercritical fluid technologies have grown in popularity in recent years, due to their low impact on the environment as well as their ability to streamline development and save costs. Louise Thomas discusses the current and future applications of this strategy for drug development.

Supercritical fluids (SCFs) are gases or liquids that are at temperatures and pressures above their critical points. At these points, SCFs have properties of both liquids and gases. Their density values are similar to those of liquids and flow properties resemble those of fluids.

SCF has been applied in a number of different ways in the pharmaceutical industry, including in chromatography, synthesis, purification and extraction, as well as drug development. In the latter context, it offers an efficient method to form end-products able to meet target specifications. It is now acknowledged as being a feasible alternative to conventional techniques using liquid organic solvents. SCF is particularly advantageous because it is safe, cost-effective and environmentally friendly.

Compared to other methods, SCF makes it easier to control product characteristics. The large number of operating parameters and conditions, such as pressure, temperature, nature of the phases in presence, compositions, flow rates, introduction modes and mixing conditions can all be varied in order to create an end product with specific properties.

Decisions, decisions

A number of SCFs are available but the most frequently used is carbon dioxide because it has a low critical temperature and is non-flammable, non-toxic and inexpensive. It also holds Generally Recognized as Safe (GRAS) status. Nitrogen oxide, ammonia, chlorofluro ethane, trifluoromethane and xenon are also relatively commonly used.

Although SCFs possess very high solvation power or solute capacity at critical points, their solubility can be enhanced by incorporating a co-solvent or a co-solute. This could be a polar or non-polar miscible solvent added in small quantities (1–5%), which would modify the polarity and solvent strength. Some examples of co-solvents used are methanol, ethanol, acetone and dimethyl sulphoxide.

The crux of the issue

There are a number of different ways that SCF can be used in drug development, in which it performs three main functions: as a precipitation solvent, precipitation anti-solvent or dispersing agent. When implementing the technology, processes are applied either to the pure drug to modify crystal morphology, habit or polymorphic form, or to the drug in the presence of one or more excipients to slow down or enhance drug release, to protect the drug during storage or within the human body after administration.

When SCF is used as a solvent, the first step involves drug solubilisation, followed by an expansion of the resulting solution in a lower pressure vessel. The dramatic increase that occurs in the solvent

power during depressurisation results in high solute supersaturations and ultra-fine particles to be formed.

The most frequently used application of SCF as a solvent is in the rapid expansion of a supercritical solution process (RESS). This is suitable for liquids that have a relatively high solubility. It is carried out within a high-pressure cell, often called an extraction or saturation vessel, which is swept by a continuous SCF flow rate. If successful, the concentration of the liquid in the SCF will reach the solubility value. If the SCF-rich phase is saturated, the resulting supersaturation achieved during depressurisation will be higher and the overall SCF consumption lower and the productivity of the process enhanced. The conditions of pressure and temperature in both the saturation and expansion vessels thus need to be carefully chosen.

A number of studies have demonstrated that RESS-type processes are a highly efficient method for coating active pharmaceutical ingredients. However, there are a number of challenges with this method. The first is that the ratio of SCF/solute is quite high. However, this can be addressed if an efficient loop of SCF purification is implemented and recycling is conducted on a large scale. The collection of generated particles is another inherent difficulty.

A potential solution is trapping the active principle solute in a fixed bed of excipient placed in the collection chamber. Finally, the enthalpy (the amount of heat and work removed from the substance) is a major engineering difficulty. Intensive heating of the depressurisation line is required to avoid carbon dioxide condensation and early solute precipitation. Although feasible to implement within a single lab, this is less feasible to achieve on a larger scale. When SCF is used as an antisolvent, the principle closely resembles that of conventional methods of crystallisation using a liquid antisolvent. In those cases, the substance to be precipitated is first solubilised in a liquid organic solvent before being put into contact with the SCF. There are several different methods using SCF as an anti-solvent, with the supercritical antisolvent (SAS) process being the most widely used. A derivative of this method, called supercritical enhanced dispersion solution (SEDS) is also relatively common.

Over the past 30 years, a number of drug solutes have been recrystallised or co-precipitated with excipients using this technique. It involves using a single vessel, swept by a continuous SCF flow rate. The solution that contains the active pharmaceutical ingredients and excipients is inserted into the high-pressure vessel using a capillary tube or nozzle.

The simultaneous diffusion of the SCF in the liquid solution and the organic solvent result in solute super-saturation and its crystallisation/precipitation. The solid particles created accumulate in the high-pressure cell and are collected after depressurisation.

The SAS process offers huge potential for drug development because the crystallisation occurs under steady-state conditions, including constant pressure, temperature, fluid rates and flow rates. This results in particles that are thus more homogenous and easily replicated than those created through alternative methods. A key limitation of this method is the reliance on organic solvents. However, it is important to note that a non-toxic solvent, such as ethanol, or harmless compounds could be used. The other key challenge is the inability to achieve complete removal of residual solvent traces when low-volatile substances are used on an industrial scale. Preferentially volatile solvents are thus recommended.

Small but mighty

Supercritical carbon dioxide can also be used as a dispersing agent when it presents a particular solubility in the compounds to be precipitated. This solubilises itself in the substance when temperatures and pressure are at the right levels for it to become molten. This process, known as particle generation from gas-generated solutions (PGSS) is well suited for polymers where carbon dioxide is absorbed in high quantities, resulting in plasticisation.

The first stage of the carbon dioxide solubilisation takes place in a high-pressure vessel (often called a mixing vessel). An adaptive stirring device is required to optimise mixing conditions.

The molten mixture is expanded within a second vessel (often referred to as a collection or precipitation chamber), placed in lower-pressure conditions. This stage can either be conducted at ambient pressure or a level higher than the carbon dioxide critical level. It is often supplemented by a nitrogen and/or an air flow to promote carbon dioxide release and the dispersion of the formed particles to limit their aggregation and retention on the vessel walls. Similarly to the RESS process, the temperature of the mixing vessel, collection chamber and pre-expansion tubing require careful consideration and control to ensure a smooth procedure.

Compared with RESS and SAS processes, this technique is advantageous because it requires a much smaller quantity of SCF. However, contrary to the SAS process, there is not a requirement for organic solvents. Despite these benefits, there are also several limitations. For example, tube clogging can occur during expansion and it can be difficult to recover the particles obtained from an expansion stream. Precipitation also occurs during the depressurisation phase, which can make it more challenging to predict the end-product characteristics and to rationalise results from experiments. ▶

Onwards and upwards

Although SCF has been used for drug formation in the industry for the past 30 years, it has yet to be widely implemented. A key factor is the inherent problem of scaling up these processes. Particle collection is an ongoing issue, made more complex by the requirement for procedures to meet good manufacturing practices (GMP) guidelines while maintaining efficiencies. One strategy to overcome this is the use of a filtration bag to collect particles in the precipitation chamber.

In anti-solvent processes, the use of an organic solvent can remain present as residual traces in the end product. However, this can be eliminated by washing the solvent after precipitation. It is important to ensure the powder is evenly distributed in the precipitation cell to avoid carbon dioxide flowing in preferential paths, resulting in less efficient washing and the formation of particle aggregates. This can be particularly problematic when working on larger scales. One option is to alternate washing with a SCF flow through the top and bottom of the cell containing the powder.

Two key considerations are needed when recycling: the quantity of the fluid to be recycled and the fluid recompression. Generally, as much as 98% of a SCF can be recycled. The SCF/solute ratio, which varies the process being used, has an impact on the ability to recycle and on the choice of equipment. For example, when the SCF/solute ratio is low, such as in the PGSS processes, the SCF cannot be recycled. At higher ratios, and in SAS and RESS processes, the fluid must be recycled.

New directions

Now that SCF for drug particle generation has been validated, future work should look to explore other processes, which can be used in combination. For example, supercritical extraction of a compound of interest from a dry natural product could be coupled with one of these processes, following the extraction stage in a separation vessel. This would eliminate the need for an organic solvent.

The use of service providers to help with scaling-up could facilitate the creation of clinical and even commercial batches. This allows for product development without having to make large investment costs. In addition to the inherent environmentally friendly nature of the processes, such activities are likely to expand the use of SCF throughout the pharmaceutical industry over the next few years. ●

Transform challenges into fresh opportunities

Chemspec Europe 2019 is set to take place on 26–27 June 2019 in Switzerland. The chemical industry hub opens its doors to global innovators throughout the field, to exhibit current changes within the market.

Operating in a highly competitive market with complex environmental guidelines, the fine and speciality chemicals industry is currently experiencing a multitude of pressures while benefitting from high levels of investment. With the right mindset and information, the current challenges can be turned into opportunities for innovation and consistent business growth.

Now in its 34th edition, Chemspec Europe 2019 unites an impressive array of experts, scientists, managers and thought-leaders, and provides a powerful and well-known industry platform to discuss the latest results in research and development, technical innovations, opportunities and regulatory issues in this rapidly changing market. Exhibitors at the exhibition are manufacturers, distributors, regulators, equipment suppliers, raw materials suppliers, traders, agents and consultants, featuring the full spectrum of fine and speciality chemicals for various applications and industries.

The highlights

Additionally, an outstanding seminar programme provides further knowledge of major industry developments, as well as key strategies adopted by industry leaders to succeed and grow. A special highlight is the Pharma Outsourcing Best Practices Panel. Chairing this event will be Dr Magid Abou-Gharbia, associate dean of research at Temple University and director of the Moulder Centre for Drug Discovery, together with Dr Rudolf Hanko, board member and former CEO of Siegfried.

Chemspec Europe 2019 will take place on 26–27 June 2019, in Hall 1 of Messe Basel, Switzerland. The Basel region is one of Europe's major hubs for the fine and speciality chemicals industry, and borders three of Europe's strongest countries in this sector. ●

For further information

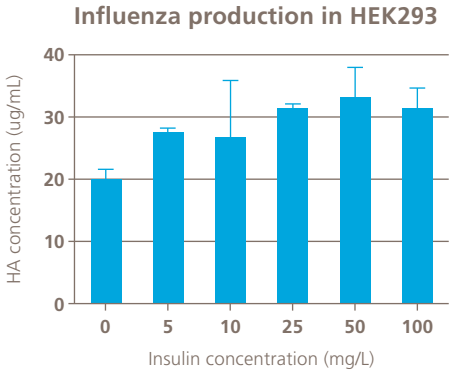
www.chemspeceurope.com

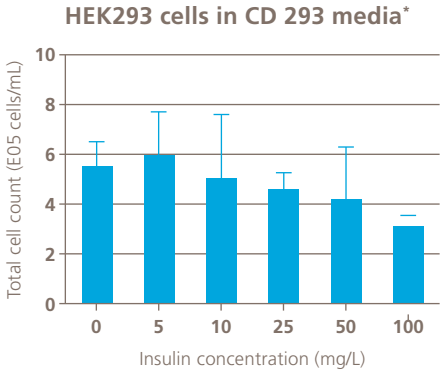
Consistency. Proven

Increase specific Influenza production with recombinant human insulin

The vaccine industry is challenged to produce large quantities of vaccines in a rapid and cost-effective way. Major changes to current bioprocesses are both difficult and very expensive to implement. Using HEK293 it has been demonstrated that addition of recombinant human insulin to commercially available chemically defined media, can be used as a supplement to increase VCD and specific viral yield.

To learn more visit www.novonordiskpharmatech.com





*Data kindly supplied by Aziza Manceur, National Research Council Canada. Hemagglutinin (HA) assay is used for quantification of Influenza (H1N1). Insulin Human AF used in the experiments is supplied by Novo Nordisk Pharmatech. CD 293 media is trademark of Thermo Fisher Scientific.

Novo Nordisk Pharmatech A/S

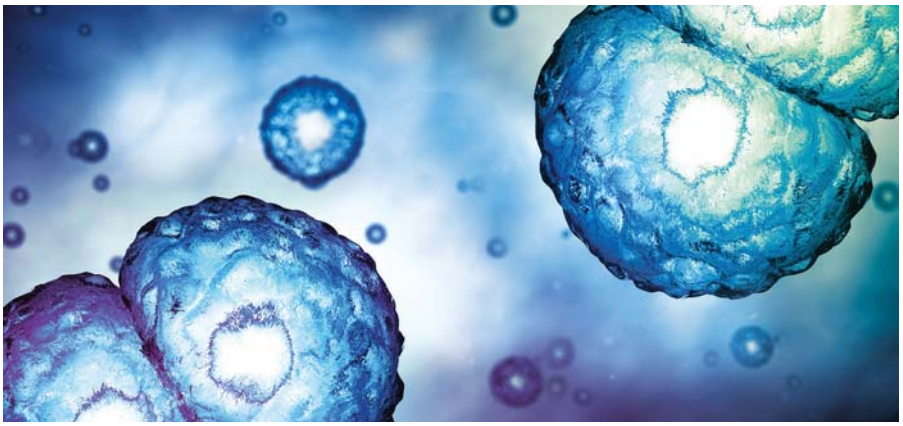
novo nordisk®

Increase specific influenza production with recombinant human insulin

Vaccines must be made in large quantities rapidly and cost-effectively. Aziza Manceur, Sonia Tremblay and Sven Ansorge from the Vaccine Program at the National Research Council Canada, with help from **Novo Nordisk Pharmatech**, discuss how production can be boosted by adding insulin to HEK293 cells to increase influenza virus yield.

Major changes to current bioprocesses are difficult and very expensive to implement. It has been demonstrated using HEK293 cells that adding animal-origin-free human insulin to off-the-shelf, chemically defined media can be used as a supplement to increase VCD, productivity and specific viral yield.

Mammalian cells are considered an alternative to eggs for the production of influenza vaccines. HEK293SF-3F6 is a suspension GMP cell line that grows in serum-free media. Using this cell line, influenza production has been achieved in shake flasks, microbioreactors and 3–7L bioreactors. In this project, insulin was added to the cultures in order to accelerate the bioprocess and boost influenza production.



Adding insulin, which is known to stimulate cell proliferation, is an effective means of boosting influenza production.

Trial by media

HEK293SF-3F6 cells were grown in two types of media: one developed specifically for this cell line (IHM-03), and another in a commercially available media (CD293). Cells were infected with H1N1/A/Puerto Rico/08/34 or H3N2/A/Aichi/8/68 in a 24-well microbioreactor cassette. Next, 5–100mg/L insulin was added. After 48 hours, supernatants were collected and haemagglutinin (HA) was quantified. HA is a highly expressed glycoprotein at the surface of the virus and it was quantified by dot blot using pan-HA monoclonal antibodies (mAb) developed in-house. As opposed to strain-specific antibodies, pan-HA mAbs have successfully probed more than 40 different influenza strains including influenza A and B types. Adding insulin meant that maximal cell density was reached sooner. Overall, a concentration of 25mg/L insulin provided an increase in influenza yield, regardless of the media or viral strain used: the yield of H1N1/A/Puerto Rico/08/34 in IHM-03 was increased almost twofold, while the production of H3N2/A/Aichi/8/68 increased by 150% in CD293 media.

A concomitant activation of signalling pathways associated with cell survival (PI3K-Akt pathway) was observed.

Stimulating effect

Insulin is known to stimulate cell proliferation and it has cell survival effects. It also acts on cellular signalling pathways that are exploited by the influenza virus. Adding 25mg/L of insulin is an effective way of increasing influenza production and can easily be implemented in a vaccine bioprocess. Evaluation of the effect of insulin on the production of other viruses and viral vectors is in progress.

Novo Nordisk Pharmatech is the leading supplier of recombinant insulin, which is sourced directly from Novo Nordisk, the world's largest producer. Its recombinant insulin is a key component in serum-free growth media for mammalian cells and approved by regulatory bodies worldwide, including the FDA and EMA. The company's products are manufactured to cGMP standards, and have distinguished record for global regulatory compliance, consistent high quality, extensive regulatory documentation, continuous availability, secure global supply chain, and high levels of service and support. ●

For further information

www.novonordiskpharmatech.com

Power to the people

Over half of the states in the US now have legalised cannabis in some form and, since November 2018, it is available on prescription for certain conditions within the UK NHS. However, due to the complex, evolving regulatory landscape, navigating this market can be challenging. **Josh Fegan**, CEO of Althea, speaks to Louise Thomas about the key considerations.

In June 2018, the case of 12-year-old British boy Billy Caldwell – whose mother attempted to bring home a cannabis oil from Canada to treat his epilepsy – brought to the fore a worldwide debate on whether families should be able to access cannabis-based preparations to treat their children.

As the story unfolded, the US FDA licensed the first cannabis-derived medicine – Epidiolex (GW Pharmaceuticals) – for the treatment of Lennox-Gastaut syndrome or Dravet syndrome in children aged over two years. In other countries, pharmaceutical-grade cannabinoid medicines are already available, such as Sativex (Bayer) for the treatment of multiple sclerosis. After the approval of Epidiolex, FDA commissioner Scott Gottlieb released a statement expressing the importance of conducting high-quality clinical trials to prove the safe and effective medical uses for the active chemicals within these elements.

Blaze through the annals of history

Although medicinal cannabis might seem new, it has a long tradition in Western medicine. The plant's natural components called cannabinoids have been used for decades for the treatment of seizures. In the 1840s, the effectiveness of hashish in treating a child with a convulsive disorder was described by physician William O'Shaughnessy following observations made in Bengal. In 1980, researchers reported anticonvulsant benefits in a trial of cannabidiol (CBD). A number of studies have also highlighted the safety and effectiveness of CBD for treating patients with epilepsy who do not respond to traditional approaches.

The different ways that cannabis-based products for medicinal use (CBPMs) are produced adds a further layer of complexity in getting these products approved for use with patients. There are many varieties of marijuana used in the manufacturing of CBPMs. Mostly these plants can be classified into two main genetic types: *cannabis sativa* or *cannabis sativa forma indica*. Sativa plants, which primarily originate from South America, are taller and have longer leaves, typically producing a more energetic 'high'. Indica plants, which come from various areas of Asia, are shorter and have wider leaves, and tend to produce a more calming, sedative effect.

Most CBPMs sold worldwide are hybrids of these two plants, created by breeders to provide specific therapeutic effects. These plants all have different levels of THC, CBD, other cannabinoids and mixes of terpenes (which also have therapeutic effects although these are currently not well understood). In addition, there are more than 80 active components in the plant. THC is the main psychoactive element, while CBS is the main non-psychoactive element. A variety of types of products are thus on the market, with dispensaries in the US offering several dozen at any one time.

It will likely be a while before the FDA approves other cannabis-derived products are on the market. For health conditions such as multiple sclerosis, anxiety and pain, the research progress has been slow. The lack of adequate, large-scale clinical studies is primarily because of the legal restrictions scientists face in getting funding for their research. In addition, the findings of of whole plant products are difficult to interpret because of differences in product composition, dose and administration protocols, and the lack of long-term follow-up. However, despite these challenges, it is an area of market likely to grow in future years and worth consideration

Leaps and bounds

In February 2019, Althea, the Australian manufacturing partner of Aphria, launched CBPMs in the UK, alongside a medical education platform for doctors to help improve patient access. Josh Fegan, CEO of Althea, founded the company in 2016 following the registration of the ND Amendment Act, an act which legalised medicinal cannabis in Australia. ▶

4

Number of CBPMs in Europe.

European Medicines Agency

Althea has successfully developed a number of CBPMs. In Australia, where the company is based, they are accessible cannabis oils and dried flower products. These can be used in a number of different ways by patients, such as being vaporised or making them into teas. The various forms are not only a matter of preference but also have different impacts on the body. For example, vaporising a dried flower has immediate onset whereas cannabis oil products take approximately 45 minutes to take effect.

Like all companies developing CBPMs, Althea has had to deal with a variety of hurdles in getting its products to market. "One of the biggest challenges for the industry is navigating the unique and complex regulatory environments between different countries or even states to provide access; it means that what is true in one market may not be in another market," explains Althea's CEO, Josh Fegan. "An absence of supporting clinical evidence can also make it difficult to raise awareness of these products and their potential to treat different conditions."

In an attempt to overcome these barriers, Althea will be releasing an accompanying educational tool to help improve patient access to their products. "Regulation also has an impact on research and development into CBPMs, which in turn can have an impact on how healthcare professionals view the products," says Fegan. "We will be launching Althea UK Concierge, a medical education platform for healthcare professionals, which helps to streamline the prescription process for specialist doctors in the UK. The platform offers access to clinical evidence on cannabis-based products for medicinal use."

Engaging in dialogue with a variety of individuals and organisations is another important strategy to drive progress in this space. "It is vital that the industry collaborates with healthcare authorities to share knowledge and expertise, and continue to build the evidence base in this space," says Fegan. "There is also an important role for patient organisations, as we have seen in the UK where they have been instrumental in driving legislative change to create access to CBPMs for patients."

An unlikely occurrence

Currently, there are only four CBPMs in Europe that have been approved by the European Medicines Agency (EMA). All are pharmaceutical products, containing defined active components including THC and CBD in specific amounts. However, the levels in these products are too high for consumption by children, leaving a large gap for young patients with conditions that could be aided by CBPMs.

Despite hesitancy among regulators and healthcare professionals, there is growing public demand to make CBPMs more accessible, as well as calls from patient organisations, such as the Royal College of Nursing in the UK. Such efforts have included the suggestion that these products should not be subject to the same level of scrutiny as other prescription medicines. This is unlikely to occur in countries with publicly funded healthcare systems, where an evidence-based approach is highly valued. In in the UK, the National Institute for Health and Care Excellence (NICE) reviews both clinical and economic evidence on new pharmaceuticals to decide which should be given to patients.

CBD and THC are the two leading cannabis-based compounds. The two share an almost identical molecular structure.

Currently, these products are only being considered in exceptional circumstances. "In England, current guidance from the NHS states that CBPMs are only likely to be prescribed for children and adults with rare, severe forms of epilepsy and for adults with vomiting or nausea caused by chemotherapy when other treatments were not suitable or hadn't helped," says Fegan.

There is certainly not consensus about current healthcare regulation within the UK. In recent years, NICE has been increasingly criticised by academics for being too focused on large randomised controlled trials to produce evidence, discounting professional expertise, to the detriment of patient needs. A 2014 paper published in the *BMJ* expressed this sentiment and it has been subject to heated debate since.

For the time being, NICE plays a hugely important role in regulating products for patients in the UK. With the organisation expected to publish guidelines about CBPMs later this year, practices within the NHS could soon be subject to significant changes.

Other countries have adopted a similarly cautious approach. In Germany, for example, doctors are only allowed to prescribe government-approved CBPMs on a compassionate basis to severely ill patients with specific illnesses who have not benefitted from other treatments. Some areas have much less tightly regulated systems. In the US, boundaries between medical and recreational use have become increasingly blurred, and cannabis-based products have been presented as a panacea for a range of clinical conditions, as well as promoted for general health and well-being.

In light of the increasing evidence base and patient demand, this market is likely to continue to grow over the next several years. Although the regulatory environment is complex, this is not unique to cannabis-based products. With a collaborative approach, it can be navigated. ●

The current legal status of medical cannabis worldwide

Countries that have legalised the use of medical cannabis include Australia, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Israel, Italy, Jamaica, Luxembourg, Macedonia Malta, the Netherlands, New Zealand, Peru, Poland, Portugal, Sri Lanka, Thailand, the UK and Uruguay.

Other countries have more restrictive laws allowing for the use of specific cannabinoids only, such as Brazil and France, which have approved the use of Sativex.

The countries with the most relaxed policies are Canada, Uruguay and the Netherlands, where cannabis can be purchased without need for a prescription. In Mexico, the THC content of medical cannabis is limited to 1%t. The same limit is also applied in Switzerland although no prescription is required to purchase. In the US, the legality of medical cannabis varies by state.

Cannabis is in Schedule IV of the United Nations' Single Convention on Narcotic Drugs, which makes it subject to special restrictions. Article 2 provides for the following, in reference to Schedule IV drugs.

"A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party."

The convention permits countries to decide whether they want to outlaw cannabis for all non-research purposes, depending on health and welfare concerns. The regulation demands that states that permit the production or use of medical cannabis must operate a licensing system for all cultivators, manufacturers and distributors, and ensure that the total cannabis market of the state does not exceed that required "for medical and scientific purposes".

INNOVATIVE HEMP SOLUTIONS

SUPERCRITICAL CO_2 FLUID EXTRACTION

FULL SPECTRUM CANNABINOIDS

HIGH QUALITY GUARANTEED

Pharma Hemp®

YOUR PREMIUM CBD PARTNER

www.pharmahemp.si | www.pharma-lab.eu

Add-on treatment with a hands-on approach

Dr David Neubauer of the Children's Hospital at University Medical Centre, and of the Medical Faculty at University of Ljubljana, Slovenia, in collaboration with **PharmaHemp**, discusses the benefits and future development of administering CBD-based medication to children.

There are more than 140 known phytocannabinoids in the cannabis plant; however, the best known are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). The first of these, CBD, has no negative psychotropic effects. In fact, it even works against unpleasant psychotropic, and other subjective and physical effects of THC, mediated by the CB1 receptor in humans.

Blaze a trail: new evidence on display

Today, there is compelling evidence for cannabis-based products' effectiveness in the treatment of refractory childhood epilepsy and certain syndromes. Single-molecule CBD is the first cannabis-derived medication that has approval from the US Food and Drug Administration (FDA), and will soon also be approved by the European Medicines Agency.

However, there are many recent studies proving the superiority of whole-plant extracts or CBD-rich extracts over single-molecule CBD, because of the synergistic effect of all the substances in the cannabis plant (together with the cannabinoids, there are also flavonoids and terpenes), which is related to the so-called 'entourage effect'.

The next step: CBD levels up

There are also other CBD that are currently in the process of becoming pharmaceutical products for the treatment of epilepsy, that are still in the pipeline, such as cannabidivarin (CBDV), delta 9-tetrahydrocannabivarin (TCBDV) and delta 9-tethrahydrocannabinolic acid (THCA), and it seems that their efficacy will also be proven.

CBDA is the CBD compound's precursor. Just like THCA turns into THC when heated or aged, CBDA decarboxylates to CBD. Found in raw cannabis, CBDA can provide numerous health benefits, thanks to its natural anti-proliferative, antioxidant, antibacterial and anti-inflammatory properties. CBDA does not stimulate the endocannabinoid system quite like its precursor does, and until now there was no report of its anticonvulsive effects.

Dr David Neubauer, Children's Hospital

CBD is now thought to treat childhood epilepsy.

The results are in: an abject improvement

All patients were treated with two standard AEDs and also received medicinal-grade cannabis products from the whole plant, such as Haleigh's Hope and Charlotte's Web. The CBDA product contained CBDA at 9%, CBD at 3.3%, CBG cannabigerol (CBG) at 0.1%, THC and THCA, each at 0.2%, cannabinol (CBN) and THCV, at 0.03% each, and cannabichromene (CBC) at 0.1%.

"There is compelling evidence for cannabis-based products' effectiveness in the treatment of refractory childhood epilepsy and certain syndromes."

Keep tabs: an experiment in epilepsy management

During the past year, the department has followed five children with extremely refractory forms of epilepsies, who have already tried from five to nine different standard anti-epileptic drugs (AEDs), were not candidates for epilepsy surgery and were not suitable for other forms of epilepsy treatment, like vagal nerve stimulation and the ketogenic diet.

Each child has had genetic epilepsies/encephalopathies: two Dravet syndrome with confirmed SCN1A mutation, 1 PDHC19 mutation (so-called Dravet-like syndrome), one CDKL mutation and one Sturge-Weber syndrome. CBDA was added to their treatment because of a deterioration in cognition and motor abilities, as well as more frequent seizures.

Within one to two weeks, the parents observed an improvement in mood (in three children), better motor abilities (in four children) and less-frequent (around 50%) and less-severe seizures (in all five children), and better sleep (in two children). One can postulate that the add-on treatment with whole-plant cannabis, enriched with CBDA, can be beneficial to children with resistant epilepsies. ●

The author would like to thank the collaborating partner, PharmaHemp, for its support.

For further information

www.pharmahemp.si

Do what comes naturally

Long before everybody was talking about hemp in Europe, the founders of **Deep Nature Project**, Andrea Bamacher and Elke Moritz, recognised the advantages of this versatile plant. For 12 years, the pair, hailing from Austria, have been engaged in the organic cultivation of hemp and the production of organic products.

Deep Nature Project and its organic hemp brand MEDIHEMP process the phytocannabinoids – found on the leaves and the flowers of the hemp plant – into rich extracts. The company specialises in whole extracts and premium extracts of the hemp ingredients cannabidiol (CBD) and cannabigerol (CBG). These non-psychoactive hemp ingredients are valued for their benefits in many physiological balancing processes in the human body. What is the ultimate aim? To make the old cultivated plant accessible to people again and help them to stay active and healthy.

From plants to riches: process leaves into concentrated ingredients

Founder and CEO Andrea Bamacher is an advocate for full spectrum extracts. That's why MEDIHEMP and CBG oils are characterised by their harmonious spectrum of natural plant substances which are cannabinoids, terpenes and flavonoids, among many more.

"Compared with pure substances, the full-spectrum extract has all the good ingredients, and through this a broad spectrum efficacy. This leads to a higher biological activity – the so-called entourage effect – and to particularly good bioavailability," Bamacher explains.

MEDIHEMP extracts are dissolved in finest, cold-pressed hempseed oil, which is rich in omega-3, as well as omega-6 fatty acids, numerous vitamins and healthful minerals.

"Compared with pure substances, the full-spectrum extract has all the good ingredients, and through this a broad spectrum efficacy. This leads to a higher biological activity – the so-called entourage effect – and to particularly good bioavailability."

Every step of the chain: maintain consistency with hands-on efficiency

There are not many producers that can claim for themselves to have the whole production process under their chain. Deep Nature Project is one of very few in Europe. "We know exactly where the raw materials for the products come from and how it is made," says Bamacher, with an understandable sense of pride.

As important as the high-quality plant material that it achieves through cooperation with local organic farmers, are the company's quality standards. Every MEDIHEMP product is analysed internally, and tested and certified by external laboratories according to strict criteria.

All products are guaranteed free of heavy metals, pesticides and certified according to an Austrian control office that facilitates the monitoring of all organic products.

Take control of proceedings: independently managed to flourish worldwide

The controls begin on the field with THC analyses. Production at the company's headquarters is in accordance with IFS Food Standards. "Analysis from our internal laboratory are continuously monitored by several external institutes," states Bamacher.

The success speaks for itself. In the meantime, the Deep Nature Project delivers its organic food and supplements to 27 European countries. All MEDIHEMP products have an official marketability certificate from an independent appraiser. This guarantees product safety as a dietary supplement for the European market. ●

Andrea Bamacher provides high-quality products in collaboration with local organic hemp farmers.

For further information

www.deepnatureproject.com

Naturally
healthy. Naturally
hemp.

AT-BIO-301
EU agriculture

Organic
Hemp Extracts

The whole plant for the immune system.

Rich in cannabinoids, flavonoids, terpenes, phenols, unsaturated fatty acids, vitamins and minerals. Our gentle CO_2-extraction method guarantees a particularly rich hemp extract with a high density of natural ingredients.

deepnatureproject.com

MEDI HEMP

www.medihemp.eu

FIRST LINE: DATWYLER'S MOST ADVANCED MANUFACTURING STANDARD

Datwyler's First Line manufacturing standard is the most advanced manufacturing concept in the industry. Designed to provide our customers with the highest level of quality and safety, First Line is Datwyler's solution to the ever-changing needs of the biotech and pharmaceutical markets. With First Line, we can help improve patients' lives.

www.sealing.datwyler.com

DATWYLER

Targeted delivery

For 100 years, humankind has struggled to effectively administer biologic drugs through pills, as large molecules are vulnerable to the ravages of the digestive system. With solutions on the horizon, Tim Gunn speaks to **Mir Imran**, inventor of RaniPill, biosimilars pioneer **Sarfaraz Niazi**, and patient advocate **Stephen Murby** about whether the arrival of oral macromolecules can change the sector.

There is a brand-new method to distribute medicine. The local post-sorting centre's launch countdown just reached 'one'.

A little while earlier, a purple package began its journey down a long, steeply sloping tube into the warehouse. About five minutes ago, it cleared a stringent set of checks and rechecks without sustaining any damage. At 'zero', a second tube peels away the formerly secure outer wrapping and fires its innards up and away to the waiting world. Someone's medicine is out for delivery, blasting in a long arc through the pre-dawn twilight. Closer in, the sudden acceleration has triggered a pinch valve, precipitating a chemical reaction that pushes carbon dioxide into a small balloon attached to a carton of pills. Soon enough, the odd contraption is floating smoothly on the breeze. Then the balloon pops. This is meant to happen. No one carries medication to a patient's doorstep on a tiny airship. But they do use the air pressure contained within the tiny airship to fling it there. And there it goes, skimming neatly through the letter box.

In this near-future scenario, the pack that lands on the doormat contains 30 RaniPills – devices that make it possible to orally administer biologic drugs. Here in the present day, Rani Therapeutics just announced the positive results of the first study into the safety and tolerability of the capsules in humans. However much it sounds like a Rube Goldberg space shuttle, the process described above is a general analogue for how each 'pill' works – just imagine it taking place inside you.

The first attempt to deliver a macromolecule drug (insulin) orally was abandoned in 1923. We've been failing to do so effectively ever since – biotechnology revolution notwithstanding. Made entirely of food-grade materials, RaniPill capsules have got this far because they bypass the stomach acid and gut enzymes that have waylaid the more than 100 previous attempts. They remain whole until the enteric coating dissolves in the intestines, which starts a chemical reaction that produces carbon dioxide. In turn, this inflates a small balloon. Finally, instead of depositing a box of pills, the balloon presses an absorbable sugar needle containing a solid form of the biologic payload into the intestinal wall, deflates, and is safely passed out. The user, meanwhile, feels nothing.

Although the lack of sensation wasn't conclusively demonstrated until the recent in-human trial, Mir Imran, RaniPill's inventor, had some idea of what the results would be. "I took more than half a dozen of the capsules before we tested them in subjects

88%

Patients would likely switch from Humira injections to a once-daily biosimilar pill.

Rani Therapeutics

because I wanted a first-hand feel," he says. "I was pretty confident going into the study."

Inside out

Imran may have swallowed more examples of an important new drug delivery focus area than anyone else alive. RaniPill, which is supported by investments from Novartis, Takeda, and Alphabet's venture capitalist arm, among others, is just one of numerous recent attempts to develop less invasive and more comfortable ways of injecting biologics and biosimilars. Indeed, shortly before Rani Therapeutics announced the results of its human safety and tolerability trial, Novo Nordisk-sponsored scientists at MIT published preclinical data from animal tests for an oral insulin delivery system that injects a solid form of the biologic into the stomach lining. If successful, these projects could have profound implications. By using the form-factor of pills to deliver an intramuscular injection to the intestinal wall, Rani Therapeutics increased the bioavailability of biologics in animal models by 10–20% over traditional subcutaneous injections. To put that in perspective, Israeli-based Oramed is running clinical trials for the most effective oral insulin formulation ever, which requires up to 69 times the amount of insulin per dose to achieve the same results as needle-based methods.

Even without the potential cost reduction, Oramed's formulation still offers a great deal of value for diabetics. People will do a lot to avoid injecting their medicine. In a study commissioned by Rani Therapeutics, more than 62% of patients and 86% of physicians reported that patients either skip injections or consistently fail to inject the drug as prescribed. Even more starkly, over 20% of rheumatoid arthritis sufferers responding to a separate 2012 survey indicated that they would not consider using a medication that required them to self-inject.

Recently, two linked ethnographic studies into the lived experience of self-injection have also shone a light on the personal struggle many patients face in meeting their biologic prescriptions. The combined review paper concluded that "patients viewed using a needle as an unnatural, transgressive act" and "did not consider the device part of the therapy, drawing a distinction between the drug, which helps them, and the device, which hurts them".

Creating the conditions for patients to think otherwise is vitally important to improving their outcomes. The closer a patient comes to adhering to the prescribed dose at the prescribed frequency, the more slowly their condition will progress. Reasonably enough, a medicine's effectiveness is determined by whether patients use it. Importantly, Rani Therapeutics' study indicated that 70% of rheumatologists and 92% of gastroenterologists think that transitioning from injections to a pill would significantly increase patient compliance rates. It's no surprise that a recent paper on the subject announced

that, "oral delivery of biologics is considered a 'panacea' in drug delivery".

From another angle, Imran thinks his product is part of a 'perfect storm' threatening reference biologics with expiring patents. Abbvie's $19.9 billion blockbuster Humira is foremost among them.

As the world's most profitable drug, Humira accounted for almost two thirds of Abbvie's $32.75 billion revenue in 2018. Moreover, two thirds ($13.7 billion) of Humira revenue comes from the US market. Even there, where patients and physicians remain suspicious of biosimilars, Rani's study indicates that 88% of patients and 86% of rheumatologists and gastroenterologists would likely switch from Humira injections to a once-daily adalimumab biosimilar pill if one existed.

That's a stunning statistic. Compare it to this anecdote from biosimilars developer Professor Sarfaraz Niazi. While speaking at a recent Pfizer conference on off-patent biologics in the US, he asked the 500 primary care physicians present whether they trusted FDA decisions regarding the medicines' safety. Responding on their phones, around 70% said no. "Some of the responses totally shocked me," he recalls. "One said that without extensive clinical study, there's no way to prove that biosimilars will not kill patients."

Evidently, Rani Therapeutics and Niazi were not dealing with the same doctors, and any comparison between a peer-reviewed study and an impromptu conference survey is limited, to say the least. Still, it's clear the connection between patient compliance and patient outcomes has the potential to reconfigure the ongoing debate around biosimilars in the US.

But for what cost?

Until now, arguments in favour of approving biosimilars to compete with reference biologics have focused on stressing that they offer equivalent safety and efficacy at far less cost. They've been directed at governments and payers over patients and physicians. As the US shows, that strategy has only been partially successful.

For Stephen Murby, biosimilars spokesman at the International Alliance of Patients' Organizations, the drugs might actually be more controversial as a result. "The more you try to sell to government based on cost," he says, "and the more government tries to force prescribers to prescribe based on cost, the more people's backs get up, and the more people go, 'I smell something rotten in Denmark'."

Patients in the aforementioned ethnographic studies into self-injection seem to have sensed something similar. A number complained that rather than being treated and talked to as people, they were quickly issued with a prescription and left to work out how to use their injector pens by a painful, lonely process of trial and error. The paper concluded that this negatively impacted both the way they took their medicines and how they perceived their care. The healthcare professionals interviewed had "little understanding of how patients managed the fear and anxiety of self-injection".

Mir Imran presents his RaniPill, a landmark technology for patient self-administration.

However, by competing in terms of patient experience, large molecule drug developers have a chance to refocus the discussion on care, rather than cost. "Engage the prescriber, the dispenser and the consumer early in your business plan," urges Murby. "Patients' organisations are not against biosimilars, but they are against being forced to take them on the grounds of cost."

As well as collaborating with Novartis, Takeda and others, Rani Therapeutics has already bought some of their own biosimilars with this in mind. Later this year, the first patients will receive RaniPill octreotide injections. The clinical trial will be taking place in Australia, home to one of Murby's least favourite biosimilar money-saving schemes. It's a tough place to win back patient trust. Whatever happens, Imran's still confident. "If we prove it with one drug molecule, we've really proved the platform for all drugs," he says. "You don't have to reapprove a syringe according to what medicine it's carrying." ●

Patients' experiences of self-injection

"The device reminds me that I'm sick. I hate it for that."

"I love my biologic, but I hate self-injecting. I hate it more than everything."

"It's a needle. It isn't safe is it?… It is the kind of thing that you spend your life trying to avoid. Now it is part of my life. I still hate it."

"It takes me about two days to work up the courage. I try to leave it off until I start to hurt. When the pain arrives, I know I have to inject and I spend a day or so circling the fridge. Once I have the courage, I have to just hold it in my hands for a few minutes to get over the feeling of wanting to run away."

Source: 'Chronic Disease and Self-Injection: Ethnographic Investigations into the Patient Experience During Treatment'

Putting Life into Technology

Who we are

Owen Mumford specialises in integrated design and build services from a broad range of self-injection platform devices for the pharmaceutical industry. From the first automatic lancing device to our patented self-injection devices, with Owen Mumford you have access to unrivalled experience in designing, developing and delivering solutions to help you make adherence easier for patients.

Device solutions

With more than 65 years' experience, your device is in trusted hands with Owen Mumford

From day one, we will guide you throughout the development process; at every step, you will benefit from professional and supportive project management, processes, industrialisation and production for a smooth development and launch.

Consultation

We listen to your needs to determine the best solution, drawing on our experience of multiple primary containers, formulations and therapies. From simple rebrands of an existing technology to wholly bespoke designs – **we can help you achieve your goals**.

Design

A multi-disciplinary team of professionally qualified experts ensures that design concepts **meet your exact requirements.** The thorough understanding of your end-users' needs includes the incorporation of human factors and ergonomics studies.

Develop

A close collaboration between design, production and your own team will ensure your device is designed for manufacture while **keeping patient satisfaction in mind.**

Deliver

The production of your device is **tailored to your needs** - for low-volume hand assembly to high-volume automation. We are also licensed for the final assembly of combination products.

Continuous improvement

As markets, regulations and formulations change, your device requirements can evolve. **Through continuous improvement, we can help ensure these needs are met.**

Quality assurance of 2 billion components and 800 million final devices per year

Self-Injection Devices

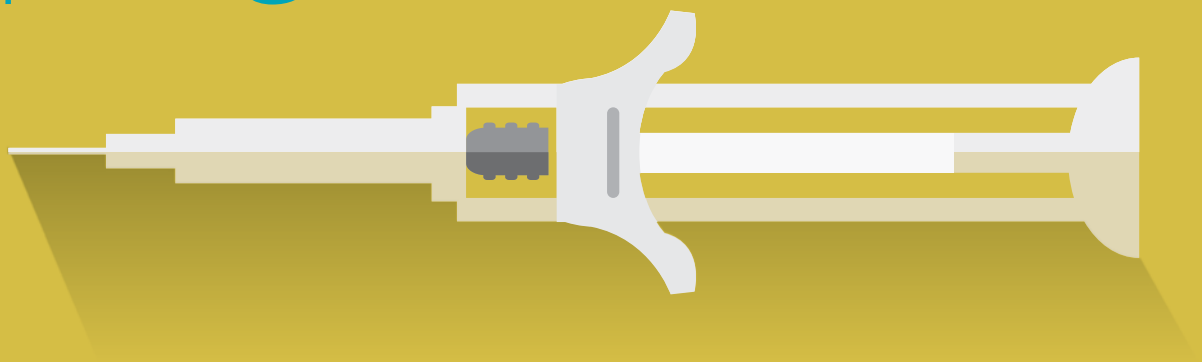
Ensuring that patients are willing and able to inject their medication is key to their well-being.
As pioneers in self-injection technologies, our experience enables us to effectively work with you to find the right drug delivery solution.

Syringe Device Solutions	
Disposable	**Reusable**
UniSafe™ Owen Mumford has developed UniSafe™, a springless passive safety device that works with standard pre-fillable syringes. This means nothing that touches the drug needs to change, which increases patient confidence when injecting and eliminates the possible risks and challenges of sprung syringes.	**Autoject®2** Reusable auto-injector proven across multiple therapy areas designed with the end-user in mind. With its ergonomic shape, it is easy to operate, and patients can inject one-handed.
Autoject® Micro Autoject® Micro Single-use auto-injector with automatic needle insertion in a compact body designed with next generation patented drive mechanism technology. Capable of supporting both button and push activation, which provides patients with a greater sense of control over their treatment.	
Autoject® Visco Autoject® Visco is a disposable auto-injector developed for high viscosity formulations. Self-priming feature at the push of a button that prepares the device prior to injection, which ensures precise dose accuracy.	**Autoject® Mini** Owen Mumford developed this simple auto-injector platform that is trusted for use with blockbusters and emerging brands alike.
Cartridge Device Solutions	
Disposable & Reusable	
Autopen®2 The first injection pen with side-button automatic delivery designed to be less intimidating than a plunger and easier to handle	

Owen Mumford Ltd.
Brook Hill, Woodstock, Oxfordshire, OX20 1TU, United Kingdom
Tel: +44 1993 812021 • **Email:** devicesolutions@owenmumford.com • **Web:** www.omdevicesolutions.com

UniSafe™

Safety is Springless



A springless passive safety device for pre-fillable syringes

Fully designed, developed and ready for commercial supply

Find out more at **Pre-filled Syringes East Coast**, Sheraton Boston Hotel

8th – 9th of April at Sheraton Boston Hotel and pick up your **Free UniSafe™ Sample**

Visit us to discover the **ecosystem built around the UniSafe™ platform**. This ecosystem meets differing users needs and offers life-cycle improvement quickly and simply.

SHL GROUP

We Bring Innovation to Life

Supporting high volume drug delivery

Bring your innovation to life with Molly® 2.25, a high-volume variation of SHL's classic Molly® auto injector, designed with improved features for enhanced production and usability.

www.shl.group

Bigger volume, better grip

The technology exhibited in the first iteration of **SHL Group**'s Molly arrived fully formed in 2010. The company now offers the improved edition, maintaining the same technology – but with more space.

In 2010, SHL introduced customers to a new drug-device development model with the preconfigured Molly 1ml. The preconfigured technology offered customers a faster development timeline while reducing costs for their combination products. Staying at the forefront of the drug-device industry, SHL has since advanced its offerings in providing Molly 2.25, which is built with bigger volume capacity yet still equipped with the same robust technology.

While biologics are expected to make up more than half of the world's top 100-selling drugs by 2020, the pharmaceutical industry is seeking opportunities to deliver highly viscous or high-volume drugs for self-treatment in a timely manner. By launching Molly 2.25, SHL addresses the rapid growth of large-molecular products, providing an auto injector that can accommodate syringes up to 2.25ml.

A new model: the next step for success

Through years of observation and in-depth research, SHL experts created a development strategy for customers seeking faster pathways to launch their auto injector project. Designers rose to the challenge of developing an easy-to-use, ready-made device with a usability focus to the patient's comfort, answering with a compact auto injector designed with preconfigured technology.

This strategy helped reduce product development time, eliminating many hurdles that developers so often encountered during the early design stage.

"Adeptly designed, the Molly 2.25 architect comes with a rectangular, easy-to-pull cap that prevents the rolling motion inherently characterised in many round-cap auto injectors."

Maintain flexibility: customise your product to fit specific needs

Molly's flexible business model offers customers the opportunity to minimise investments by cutting down major individual investments in tooling, assembly, and/or testing equipment. Customers are offered different levels of customisation, in which they choose from a selection of component designs depending on their pre-filled syringe, fill volume and drug formulation.

An additional factor that expedites the Molly auto injector production process comes from SHL's vertical integration of key manufacturing capabilities that facilitates parallel development of automation and assembly systems. SHL's in-house automation capabilities drive a robust assembly line for production scale-up, enabling SHL the capacity to meet the rapidly growing market demands. Commenting on SHL's automation systems, SHL director of automation Lucy Chung says, "Years of dedication has enabled us to produce fully- automated assembly and testing systems that will upgrade Molly's production."

Bigger yet portable: the larger size that remains manageable

Numerous usability trials reveal that users prefer smaller devices and less frequent injections. Thus, SHL managed to keep the slightly larger Molly 2.25 handy and lightweight, ensuring an easy handling experience without sacrificing patient preference. The bigger Molly owns a similar design to Molly 1ml, yet is built with a slightly larger body so as to accommodate the 2.25ml syringe. The larger size, however, is far from any notion of bulkiness, maintaining the original Molly's design feature of being portable and compact.

Adeptly designed, the Molly 2.25 architect comes with a rectangular, easy-to-pull cap that prevents the rolling motion inherently characterised in many round-cap auto injectors.

This strategic design is mainly aimed at preventing auto injector breakages from accidental drops.

Through combined efforts of designers, engineers, project managers, and business developers, the Molly 2.25 design continues to uphold SHL's high standards in the design and making of devices, while also proving SHL's ability to meet customer demands and patient needs. ●

Through the launch of Molly 2.25, SHL has again proved its ability to meet customer demands and patient needs.

For further information

www.shl.group

Development at its most durable

World-leading brand **LTS Lohmann Therapie-Systeme** has developed innovative transdermal systems in addition to its extensive work producing solutions for all stages of drug development.

Having strongly situated itself as an authority in transdermal therapy systems (LTS TTS) and oral thin films (LTS OTF), offering solutions at all stages of drug development – from feasibility assessments, research and development of new formulations to clinical trials (up to phase II), production and packaging – LTS Lohmann Therapie-Systeme is now also developing innovative transdermal systems such as microneedles and 'active' patches.

Passive suppressive: development to replace a limited technology

Passive patches that release the active substance via passive diffusion are limited to relatively small-molecule and lipophilic active substances, since only these can penetrate the skin in therapeutically relevant amounts. As a result, active substances with larger molecules, such as peptides, proteins and vaccines, cannot be administered this way. But these new, often biotechnologically produced, drugs frequently have major potential for the therapy of diseases that until now have been inadequately treated.

Pain-free injections: reduced size for decreased irritation

LTS microneedles have been developed as an instrument that is lengthy enough to penetrate the outer layer of skin but too short to irritate nerves and blood vessels.

These can be used to inject active substances with larger molecules into the skin, an application that is largely pain-free. Microneedles create tiny holes in the outermost layer of skin, that significantly increases the rate at which the active substance is absorbed.

Needle-free injection systems use a stamp-piston-system, that works with high-tech-jets to spray the aseptic liquid or drug solution with high pressure in less than one second under the skin. The micro-needle-injection system injects microscopically small needles from 100µm to 1,000µm in length into the upper layer of the skin; it is pain-free because no nerve endings are touched or disturbed. The needles consist of materials like ceramics, steel, polymeric or silicon; the active substance can be released by micropores or dissolvable needles. LTS is researching a number of different microneedles made from different materials and with different gauges, designs and sizes for a wide range of applications.

LTS has optimised its storage stability by maintaining cutting-edge concepts and delivery forms.

The active patch: pristine concepts to ensure good storage stability

Another way to increase the opportunities to apply transdermal therapeutic systems is the use of active systems via iontophoresis, for example. This involves conducting a very low electric current through the skin, that transports the charged molecules.

An iontophoresis patch consists of one unit that comprises a microprocessor and a battery, an electrode with the active substance, a counter-electrode without the active substance and the other components of the patch. This means the rate at which the active substance is absorbed can be controlled via the electric current, which is controlled via the microprocessor.

Iontophoresis enables substances that are not suitable for passive systems as a result of their intrinsic characteristics, including charged molecules, to be absorbed transdermally. LTS has managed to achieve stability by employing innovative drug delivery forms concepts. As such, this technology offers plenty of applications.

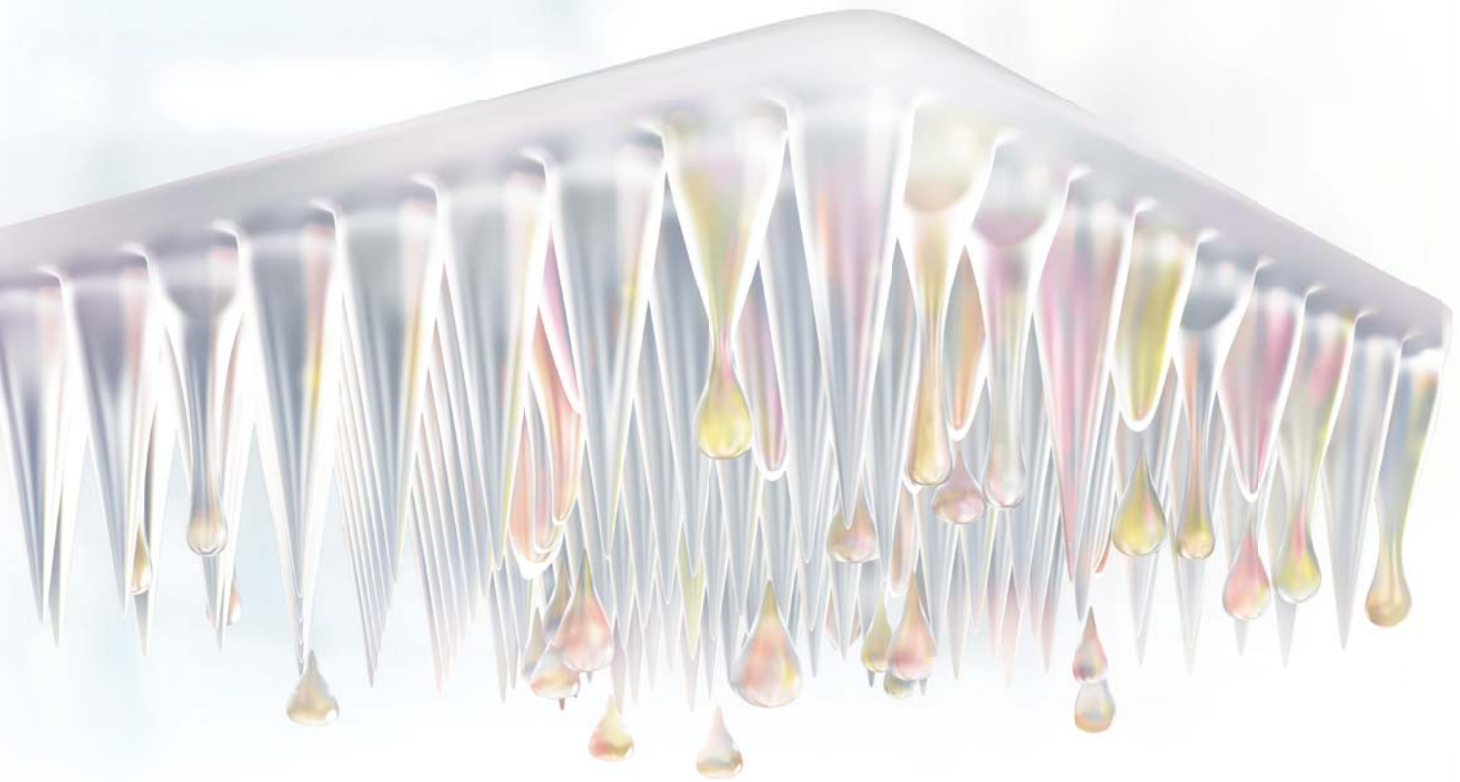
LTS is in the process of developing key solutions for issues that permeate disparate facets of the drug delivery industry. Using its expertise and wealth of experience, the company is again turning heads in its leading development and understanding of what would best benefit the industry as a whole – from distributor to supplier, to patient. ●

For further information

www.ltslohmann.de

LTS
TRANSDERMAL. MARKETLEADER.

NEW PERSPECTIVES, MORE POSSIBILITIES



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

Connected devices for daily use

Sensile Medical's innovative pump platform is detailed here, with regard to its suitability and ease of everyday use, as well as its sensational value for the product at hand.

Gerresheimer affiliate Sensile Medical develops connected platform device solutions for daily home use by patients in all kinds of therapeutic areas. Patients suffering from chronic diseases are often depending on frequent injections of liquid drug products. Familiarity with the burdens of the treatment, the disease and the specific patient needs enables Sensile to develop dedicated platforms. By focusing on patient's needs, Sensile provides solutions that support various therapies and benefits for healthcare professionals as well as other stakeholders.

Make sense of it all: focus on patient needs

With Sensile's pump platform, devices are either designed in on-body or off-body configurations. This decision is often driven by multiple factors like the total volume of administered drug product, the wear time, the patient's activity level during injection time, asl well as disease-related impairments.

These electromechanical devices are suitable for everyday use and equipped to provide supporting data to patients and other stakeholders. Cooperation with the pharma partner from day one during a collaboration is key to determining what information needs to be provided, what support the device can offer for patients and stakeholders like HCPs and payers.

In this data-driven world, one can easily lose focus and exaggerate on what can be collected instead of focusing on the treatment-related values and why the data is collected.

Therefore, Sensile has set up multidisciplinary project teams to learn about and evaluate important needs. Collecting and compiling information around treatment burdens, understanding the disease from the patient's perspective and consider the needs of the HCP in supporting the patient are important activities early in every project and continue throughout the development.

A plan in order: flexible platform for various needs

Delivering value from the supporting data is a next important step. For example, the software packages of the recently launched infusion pump device are adaptable to multiple languages, guiding all stakeholders through the device and step-by-step instruction of use.

Incorporating technologies such as RFID ensure that only the intended drug can be used with a specific pump. As such, potential use of the wrong drug or counterfeit medication can be detected. It also prevents using medication beyond its expiration date. RFID can also be used for traceability matters. These features all provide additional safety.

Some treatments require flexible dosing based on the patient's condition, such as weight-based, and day and night profiles. Additionally, allowing bolus injections by the patient are part of some treatments as well. Collecting data regarding injection volume over time with the amount and time when a bolus has been given can prove to be very valuable for patients and their HCPs. The data does not have to be recorded manually by the patient, but is saved in the device and may be transferred to a mobile phone and visualised electronically upon the next doctor's visit and discussed.

The history also serves as a reminder to the patient; for example, how many boli have been given. The HCP can store the data in his file and adapt the treatment plan accordingly.

Applying the set basal and bolus rates, the system calculates the use time for the remaining drug volume. This supports the patient in his daily planning in and outside the home or environment. Sensile continues to further develop its digital offerings connecting bridges from drugs to patients. ●

Incorporating technologies such as RFID ensure that only the intended drug can be used with a specific pump.

For further information

www.sensile-medical.com

Connected platform device solutions for daily home use

Sensile Medical – Connecting bridges from drugs to patients

SENSILE MEDICAL

A Gerresheimer Company

www.sensile-medical.com

Stick it out

More than 1,800 claims for needle-stick injuries were made in the UK in a five-year period. However, most were likely avoidable if needle-stick prevention systems had been put in place. David Callaghan speaks to **Emmie Galilee** from the Health & Safety Executive about needle-stick prevention.

Accidents do happen, and nowhere are the consequences more serious than in our health services. Injuries from needle-sticks or 'sharps', as they are commonly known by health professionals, can have very serious results such as contracting a disease from a blood-borne virus such as hepatitis or HIV.

Often, simple measures can be taken to lower the chance of someone being cut by a needle. Training and practice behaviours help to prevent a dangerous incident occurring. There are also devices attached to some needles that limit the time a needle is exposed and can harm a health practitioner or patient.

NHS Resolution, which deals with compensation claims from healthcare staff who suffer an injury, says it received 1,833 claims for needle-stick injuries during 2012–17. It says of these claims that 1,213 were successful (with 326 still to be resolved), which cost the NHS more than £4 million or the equivalent of 125 Band 5 nurses for a year.

Of the successful claims, 914 were from ancillary staff, such as cleaners, porters, maintenance and laundry staff, who were harmed because needles had not been properly disposed of. A total of 137 clinical staff made claims that attracted a pay out, with 162 from other occupations.

The main causes of injury, according to NHS Resolution, included inadequate disposal of clinical waste; non-compliance with infection control precautions; overfull sharps bins; and not using safer sharps or protective equipment.

Safety first, every time

UK law has been drafted to reflect a European directive from 2010 (through the Health and Safety Sharp Instruments in Health Care Regulations 2013), which made it mandatory for all member countries to put legal measures into place to help prevent needle-stick injuries.

Emmie Galilee, head of policy and strategy in the health and social care services sector team at the UK Government's Health and Safety Executive (HSE), says there were already laws in place requiring employers to protect their staff. The Health and Safety at Work Act 1974 and Control of Substances

Hazardous to Health Regulations 2002 cover the handling of needle-sticks, with an expectation that employers will do what is practical to reduce risks. The regulations introduced in 2013 built on the provisions of the earlier laws.

"The use of safety devices is only one element in reducing risk of needle-stick injury," says Galilee. "They are not a complete solution and injury to the healthcare worker could still occur if the patient moves unexpectedly as the procedure takes place. Information, instruction and training in safe use of equipment are very important."

There is a lack of evidence that sharps injuries have gone down, but between 2007 and 2013 there was only one sharps prosecution, in 2010, following a needle-stick incident in circumstances where an employee contracted hepatitis C.

A mixed bag

The NHS trust concerned was fined for a breach of regulation 6 Control of Substances Hazardous to Health Regulations 2002 (COSHH), failure to carry out risk assessment, and for a failure to comply with section 2 of the Health and Safety at Work Act 1974.

In 2017, research by the HSE was unable to say whether the number of sharps injuries had fallen, but said it was likely, although it added, "The conclusion is that more should be done to promote uptake and compliance with the sharps regulations."

A review carried out by the HSE from 2015–16 found that of 40 NHS organisations in England, Scotland and Wales, 95% were committing breaches of health and safety regulations, and 83% were not complying with sharps regulations. As a result of the findings, 45% were handed improvement notices by the HSE.

Typical failings found by the review included inconsistent use of safe sharps, and failure to use safer equipment that was available.

Then in 2018 a 'Post Implementation Review' by the HSE found that there was some initial resistance to using new devices, but this "dissipated". Figures released by the NHS Supply Chain showed a 65% increase in the use of 'safe sharps' from 2014–17.

But the review said, "The evidence for a reduction in injuries post regulations is mixed, with some evidence suggesting that injuries have gone down, and other evidence to suggest that injuries have remained the same."

Risky business

The risk of contamination is low, but for every health worker who suffers a needle-stick injury there is the anxiety of not knowing until tests have been done, the review says. A possible contraction of hepatitis B or C or HIV certainly affects a person's quality of life while they wait for the outcome of test results. They may also be affected by the side effects of anti-viral drugs, and be forced to take time off work due to sickness.

"It is actually quite a low risk and there has been just a handful over several years," Galilee says. "It is about reducing this as far as is reasonably practical. It is not humanly possible to eliminate risk."

Galilee says manufacturers are working on new types of needle-sticks with safety mechanisms, but there are many already available. Examples include spring-loaded needles that retract after use, or blunt-ended scalpels. There are also 'needle blocks' to accommodate needles after use.

In some instances though there isn't a safe version of the equipment available. "Then a safe system at work is needed to reduce risk, making sure people are properly trained, and are not leaving needles lying in a kidney tray exposed for anyone to accidentally touch it and injure themselves," Galilee says.

She says it is especially important to be careful in dentistry and paediatric environments. Dentists may have to keep the needle to hand to top up anaesthetic, and there is a risk of stabbing themselves when they resheaf the needle.

Take it global

In Europe, there are an estimated one million needle-stick injuries every year, and 80,000 workers infected with hepatitis or HIV.

Most countries have introduced laws or regulations to implement the EU directive, although some, such as Austria, were resistant initially because they saw it as interference.

A survey by the European Biosafety Network showed that Denmark was an exception in that it brought in guidance rather than legislation. Awareness of the law around sharps was high in the UK, Belgium, the Netherlands, France, Germany, Scandinavia and Ireland, but less so in some eastern European countries and Greece.

"The UK did a pretty good job at adopting the EU directive. Some countries have implemented it in more detail than others," says Ian Lindsley, secretary of the network. "Some countries are lagging behind in their policies.

In some cases there isn't an inspection regime to check it is being adopted, and often data on safer practices isn't available. However, Lindsley believes that awareness is higher than it was before as a result of the regulations and laws throughout Europe.

Other countries have specific problems, such as France where the district nurses are self-employed and it is difficult to direct them to change their practice. In the Mediterranean, it is tricky to order practice changes as government and health services are decentralised. The network, which was set up by the UK public

95%

Percentage of 40 NHS organisations breaching health and safety.

HSE

Steps need to be undertaken to ensure the complete safety of hospital staff.

services union Unison and the Spanish General Council of Nursing, helps to ensure the directive is implemented across Europe. "It is a universal directive based on a partnership between employers and unions," says Lindsley. "Generally speaking, in the UK and most other countries there is a consensus (supporting the directive)."

Prevention is better than a cure

Across the Atlantic, the authorities are also grappling with the issue of needle-stick injuries and how to prevent them.

In the US, the Needlestick Safety and Prevention Act 2001 lays down the requirements on employers to take every step to prevent sharps injuries to their staff, including the use of new technology.

One in five healthcare workers in the US suffers a needle-stick injury. Nurses are the most common profession in the US to be harmed by a needle-stick, with 40% of injuries. Statistics from EPINet show that more than half of the injuries occur in the patient's room or at their bedside.

The Premier Safety Institute estimates that 85% of sharps injuries are preventable. It says safety devices have a big role to play in prevention, but there can be drawbacks.

"Devices with safety features have been shown in numerous studies to reduce the frequency of needle-stick injuries, but for many reasons they do not completely eliminate it," the organisation says. "In some cases, the safety feature cannot be activated until the needle is removed from the patient. Some healthcare workers may fail to activate the safety feature; users can bypass the safety feature; or the safety feature may fail."

The institute points to a study from 2010 of practice in French hospitals showing that 'passive' safety devices, that work automatically, are much more effective than those requiring the user to trigger the shielding mechanism. It recommends that healthcare workers are involved in the selection of the devices to be used, and to be aware that they may take some time to get used to using a particular device.

It has also given guidance on the safe use of sharp containers, that stipulates that they must be puncture-resistant and leak proof. They should also be easily accessible to anyone using needle-sticks.

Some of the mistakes made by practitioners, the institute says, include, "reusing syringes, contaminating multi-dose vials with unclean syringes, using single-dose vials for multiple patients, reusing end-caps from single-use syringes, using fingerstick devices on multiple patients without cleaning, and using blood-sugar measuring devices on multiple patients without cleaning".

Large bills to be paid

Back in the UK, NHS Resolution says there are many steps employers can take to avoid staff getting injured, and for them facing large bills for compensation.

It recommends to employers to take precautions. "Check training on correct disposal procedures is up to date; review your organisation's procurement of safer sharps versus conventional sharps; consider why you are not using safer sharps," says NHS Resolution. "Check training is implemented on the use of safer sharps; review your organisation's claims for needle-stick injuries, costs and hidden costs – any extra cost of safer sharps is likely to reduce harm and the cost of legal claims."

There are many aspects of needle-stick safety for employers and staff to be mindful of and to put into practice. There will always be a risk, but there are practical steps that minimise the chance of being injured.

Safety devices built into needle-sticks are clearly a big help, and a means to prevent accidents. It needs to be remembered though that unless they work automatically, they rely on the user operating them properly.

Supply chain & logistics

Contents

Get connected

The internet of things (IoT) offers huge potential to improve efficiencies across the supply chain. These technologies provide real-time data about products and conditions, facilitating the ability to respond quickly and anticipate future issues. **Karen Taylor**, director of the Centre for Health Solutions at Deloitte, speaks to Louise Thomas about how to integrate IoT into existing systems in order to maximise the benefits of the technology.

The internet of things (IoT) is a concept thrown around a lot, both inside and outside the pharmaceutical industry. Defined as a technology that allows the tracking and monitoring of connected devices, it offers huge potential for better control of the supply chain, particularly when combined with tools such as blockchain. IoT is an umbrella term and includes a number of different options to improve efficiencies and traceability, as well as differentiation and innovation. A 2017 Deloitte report highlighted three key aims of IoT for supply chain: collecting data from real-world objects, communicating and aggregating the data into insights, and using these results to improve systems.

There are two main families of IoT devices. The first of these are 'things', are devices attached to an object, or independent devices that can behave autonomously. These are temporarily or permanently connected to a network (such as the supply chain), collecting and communicating information about its functioning. In some cases, these technologies can receive instructions to modify their behaviour based on the data they are gathering. Sensors or beacons are the second family, which are devices that take extrinsic measures of behavioural or environmental conditions and can be attached to moving objects or fixed in place. 'Things' and sensors work together.

Get to know those involved

In order to optimise the effectiveness of IoT, consideration of the whole infrastructure is important, rather than merely the network and the devices. "The IoT isn't just about technologies, it's about the integration of devices that allow you to collect data to monitor and evaluate the activities across the supply chain," explains Karen Taylor, director of the Centre for Health Solutions at Deloitte. "You've also got to have the connectivity landscape involved."

The integration aspect is key as it manages both the sensor and network elements, aggregating the data from both of these and assimilating with other data sources and preparing it for the next part in the process. Augmented intelligence takes the information gained and translates it into actionable insights that can be taken to optimise the supply chain. These can either be in real time (known as data in motion) or long-term data (known as data at rest). Augmented behaviour is the next phase that encapsulates the actions or changes in human or machine behaviour resulting from insights generated

by applications using IoT data. "The whole point of IoT is obtaining automatic collection of different information sources to be able to understand what is happening along the supply chain and that impact," says Taylor. "That includes information about the types of products, the types of pharmaceutical ingredients to the technology around developing the way that those ingredients will be provided to patients, whether that's injectables or tablet form, blister packets and those sorts of things."

There are a number of challenges faced by the supply chain. These can be addressed by combining IoT technologies with blockchain. However, it's important to acknowledge that blockchain is not merely a storage system. "Blockchain isn't just the technology to be able to trace the products as they move down the supply chain," says Taylor. "It provides that security because you will know who has been involved with that product and the different stages down its journey."

Do not adjust your monitor

Traceability is clearly one of the key ongoing issues with supply chain management, including the requirement for event monitoring and the collection of product-specific data. IoT can provide a full audit trail of data throughout the supply chain, which is beneficial for multiple individuals and organisations involved. "It's about providing that end-to-end security for both the pharma company and the clinicians who will be prescribing it, and that certainty that what they are prescribing is on the label," says Taylor. "Labelling is a particular area where IoT can have a big influence because you can have a digital based sensor label that will alert to any tampering of the supply chain."

Tracking products throughout their journey is particularly useful for those travelling through the cold chain. Deviations in temperature can easily be captured with an IoT device, the data of which can be input and tracked on the blockchain. This would then generate notifications and action can be taken to intervene in that aspect of the chain. "Being able to monitor the products that are being maintained at a certain temperature, whether they are being shipped or moved in freight, being able to collect data that the temperature that they're being kept at is at the right level, that is a really important part of ensuring the quality of the product," says Taylor.

Technologies can also be coded to perform specific tasks and trigger diverse responses depending on the conditions being measured. For example, in a worst-case scenario, if certain pre-conditions are not met drugs could be automatically pulled before being released to the market. This not only reduces the risk of non-compliance but also protects patients from adverse events.

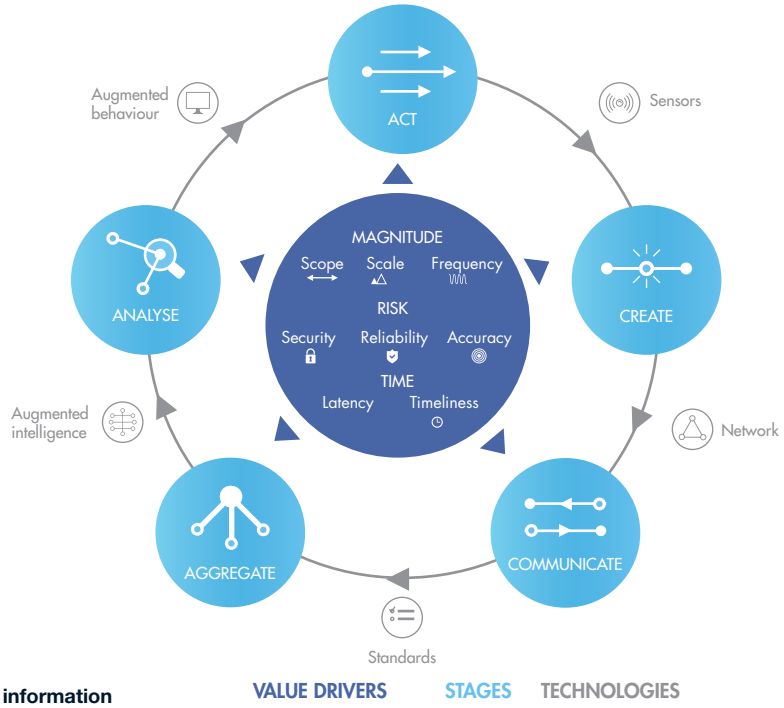
Compliance is another key difficultly that obviously needs to be evidenced to demonstrate adherence to regulations. The immutable and irremovable nature of blockchain means that a single, timestamped, tamper-proof source of data can be produced.

"Having a complete view of the supply chain and data that can demonstrate how products have progressed along it enables requirements to be met in a more effective and efficient way," explains Taylor.

IoT devices can help to capture data that could be useful to any stakeholders with credentials to retrieve the information which could be a reliable source for entities such as the FDA, which then would be able to obtain a full product history. The ecosystem could also develop its own processes to trigger and notify stakeholders whenever predefined conditions or unusual events occur.

A further challenge is flexibility; companies are faced with having to adapt to different environmental conditions in a cost-effective way. However, IoT and blockchain enable the creation of smart contracts, providing real-time rule-based verification of multi-stakeholder confirmation. "If you're monitoring a global supply chain, you've got to be able to track products across different geographies so that has to be brought into mind when you're developing a digital approach to managing your supply chain," Taylor says.

Although all of these capabilities have huge potential for optimisation of the supply chain,



The information value loop of IoT.

the implementation of the technology is still in its infancy. "How many companies have fully embraced the technology is hard to answer," Taylor says. "My understanding is that they are at the early stages of adopting this technology because it is such an expensive and global initiative."

Part of the trade

Part of the reason for this relatively slow uptake is the uncertainty around them. As acknowledged by a 2017 Deloitte paper, these technologies remain unproven. For example, blockchain is effective in securing transactions but can be limited with regard to performance, scalability and confidentiality. IoT also needs to demonstrate that its infrastructure is effective, efficient, secure and reliable. As it is an amalgamation of multiple technologies, standards will have to be defined and accepted so that they can work well together, which will take time.

Integrating IoT also demands greater crosstalk between the digital and the physical world. One of the key functions of a blockchain is sharing information on a trusted platform and the collection of this information demands a strong interconnection. A number of different strategies will need to be tested to see which is best able to seal and authenticate products effectively. This need for verification is also true of sensors, and for the resources that are calibrating and maintaining them. It is inevitable that some tough decisions will have to be made about risks versus costs when using IoT and related technologies, as well as the value of both the products being transported and the value of the data generated about them. The global nature of the pharmaceutical supply chain makes the implementation of IoT particularly difficult. Achieving complete control thus requires all stakeholders to commit to investigating and implementing these technologies. "Natural ingredients are sourced from one country, shipped to another for research and development, to another for production and manufacturing so they need to have end-to-end visibility of that supply chain and they build their systems over many years," says Taylor. "The digital technology that is now much more widely available provides an opportunity to improve the efficiency of all of those interactions but this is at the interaction phase that all the challenges exist."

Trade-offs will inevitably have to be made between transparency and confidentiality among stakeholders. While navigating these decisions, it is of course imperative that efforts are made to ensure that company strategies and activities cannot be leaked.

Where IoT is being integrated into supply chain management, vast amounts of information are being generated, which can be challenging to turn into useful insights. "The mass of data that's available means that companies have to find ways of turning that data into intelligence," says Taylor. "That's where the other parts of IoT come in, the analytics platforms, the systems and software providers that can capture all this data and turn it into insights that then allow the company to make decisions at speed to improve and intervene when necessary."

Active aggressive

Looking to the future, it is clear that IoT development will continue to evolve and gain greater momentum within the industry. "Inevitably, you will see a wider use of digital technologies to improve the efficiency and effectiveness of the supply chain, with robotics, process automation and application of AI and machine learning," says Taylor. "The systems will be iterative and improving all the time."

Taylor remains highly optimistic about the potential of these developments for the supply chain. "Improving the efficiency and productivity and will become second nature to the managers of supply chains," says Taylor. "Having this vision of an IoT will mean all these technologies have a part to play."

Although these developments won't occur overnight, they are not a product of the distant future either. "I'd say this will definitely happen within the next five years," says Taylor.

Companies cannot remain passive if they want to implement these effectively. "The development of new business models are contingent on the technologies," explains Taylor. "The fact that you are using real-world data and you've got real-time information, you will need to change working practices," she concludes. ●

New tech for all

Representatives from **BLULOG** discuss the threat of drug falsification on a global scale – a phenomena that involves counterfeit medication polluting the market and putting consumers at risk of great harm.

Drug falsification, a major threat to public health, is a global problem, and the World Health Organisation (WHO) estimates that about 50% of medicines currently sold on the internet are today falsified, meaning counterfeit medicines or remedies containing banned drugs.

Take aim at the fakes

Serialisation aims to combat this phenomenon by ensuring the ID traceability, source and history of each product – securing the drug's entire chain of distribution, from the producer to the patient.

This protection includes the integration within the Data Matrix barcode, product code, batch number, serial number and expiration date of each box of drugs.

Each reading of this barcode allows the verification of the box authenticity and traceability to its final dispensing point. The history of each phase is thus stored in European databases. Stéphane Mure, president of THERMOLABO, a company specialising in monitoring solutions for pharmaceutical companies, explains, "While this directive brings a significant improvement in terms of protecting patients against counterfeit medicines, it is regrettable that these traceability measures do not cover the qualitative dimension in terms of their conservation conditions throughout the supply chain."

Determine the genuine article

Indeed, while the digitalisation of the logistics chain generated by this serialisation now makes it possible to demonstrate the authenticity of medicine dispensed to a patient, it unfortunately cannot prove if it has been preserved in accordance with GDP and in the respect of the terms described in its marketing authorisation.

With the aim to answer this problem, THERMOLABO has invented Sensolabo. This pioneering new technology in contactless temperature-monitoring solutions dedicated to the pharmaceutical sector, was elaborated in 2017 in partnership with French-Polish company, BLULOG. Company CEO Jérémy Laurens explains, "BLULOG has been always focused on contactless near field communication technology for temperature monitoring because it provides considerable benefits from both an economic and operational point of view."

In fact, Sensolabo now makes it possible to establish, with a single gesture and without effort, an electronic link between the serialisation information and the storage conditions. The principle is simple and consists of scanning the Data Matrix code of a box using an NFC reader (such as a simple Android smartphone) and then approach the Sensolabo logger to automatically introduce the identification data into the temperature logger, itself identified by a unique and specifically implemented serial number.

BLULOG is devoted to combating drug falsification.

It creates an unalterable link between the box and the temperature data logger, the data being in parallel also automatically sent and saved on secure servers. Therefore, thanks to the search engine integrated into the associated cloud platform, temperature curves can be verified directly using a batch or box number.

Do away with the paper trail

This innovation allows very significant productivity gains for the entire quality team, that had previously manually established the link between a batch of products and a temperature data logger serial number of which was too often scribbled or illegible in paper documents. In addition, there is no possible way to physically manipulate data and therefore no risk of errors, thus it significantly improves the level of compliance of the monitoring processes already put in place. Sensolabo is adapted to all logistical configurations. It also makes it possible to scan any barcode.

"BLULOG has been always focused on contactless near field communication technology for temperature monitoring because it provides considerable benefits from both an economic and operational point of view."

Jérémy Laurens, BLULOG

For instance, DHL Global Forwarding is using this feature to link the BLULOG NFC temperature data loggers to shipment tracking numbers and integrate all data together on their tracking platform.

"This is a unique offering in the market, but we do not think about patenting it, which would limit access and use in the drug distribution chain. It was essential to us to be able to contribute on our scale to the improvement of public health," concludes Mure. ●

For further information

http://blulog.eu/en

Boundless potential, just around the bend

With the internet of things (IoT) increasingly shaping logistics behaviour, Richard Wood, technical director at **Softbox Systems**, looks at how its impact is protecting businesses, moulding the future and saving lives.

To ascertain the level of influence that the internet of things (IoT) is having on the pharmaceutical supply chain, you don't have to look much further than the coverage it currently enjoys. Narratives are plentiful. But no less prominent, it would seem, are the rates of adoption.

Bain predicts the IoT market will grow to $520 billion by 2021, more than double the $235 billion spent in 2017. In vertical terms, Statista puts transport and logistics at the top of the industrial investment tree, with a $40 billion outlay forecast for IoT next year. Where the supply chain is concerned, its capabilities are such that an inexorable march into the fold appears just a matter of course.

The new safety net: an online lifeline for product integrity

The nature and scale of the pharmaceutical industry's global expansion has changed logistics dynamics. New markets and compliance, transportation delays, the ascent of biologics, packaging, product excursions, technology, theft and human error are all challenges needing resolution. Transparency across a new super-connected supply chain, says a Council of Supply Chain Logistics report, can deal with much of this complexity, as well as the scale and distances involved. IoT, it would appear, offers a potential lifeline to product integrity and company bottom lines.

Temperature control packaging (TCP) and logistics companies have already recognised visibility and traceability as top priorities. As new strategies and ways to ensure product safety hit the radar, a new generation of monitoring practices has emerged. The most significant centres around near real-time temperature and location monitoring. Yet while these advancements have been crucial, at one end of the cold chain spectrum they have been critical.

Richard Wood, director, connected digital technologies Softbox Systems

Partnerships that save lives: survive through it, together

One of the most important developments for the substantiation of IoT technology first emerged in the aftermath of Hurricane Maria, a natural disaster that devastated Puerto Rico in 2017. As the supply chain collapsed in the country, people with serious conditions were unable to gain access to their daily medication. Week on week, the death toll multiplied. One diabetic relative of an employee who worked for a pharmaceutical giant was among the causalities and this pushed the company into action.

Partnerships were formed that married IoT technology with TCP systems. And just two years on they were flying – quite literally; a third element, drone technology, had become part of the solution.

A phenomenon gains its wings: introduction of drone technology

At the time, commercial drone development was way beyond its teething stage. There were vertical take-off and landing versions available that were useful over short distances, as well as fixed wing models, with catapult launching systems that could potentially reach areas 50 miles away.

Lightweight and powerful, these drones were already being equipped with cameras. But could they carry anything heavier, such as temperature-sensitive cargo? Back in 2008, Softbox Systems had first optimised containers for aircraft unit load devices. So why couldn't shippers be optimised for drones?

Research commenced on cargo drone – new lightweight TCP was developed; an adaptor plate was conceived for secure attachment; package temperatures were tested in labs with thermal simulation tools; and data connectivity and transmission was embedded. In just six weeks, rapid development prototyping had taken place, with cooperative work going on between relevant teams across different continents. In a final proof of concept, test flights were conducted in remote areas of Puerto Rico that had been hit hardest by Hurricane Maria.

The advantages of transparency: accuracy through openness

The emergence of this cooperative piece of innovation means biologics and other life-saving medical supplies can be housed safely inside a temperature control shipper and transported by air to any remote or devastated area on earth. But it's also the mechanics behind this innovation that are opening doors to the future.

To maintain the safety and quality of the medicines, the Skypod temperature control shipper, as it's known, includes a Smartbox device powered by IoT technology. It gathers near-real-time data including location, and shipper temperatures, external and internal. A temperature-monitoring tag is paired via Bluetooth enabling data to be sent to a SIM card gateway. Once transmitted to

The future of the industry will rely heavily on the proper integration of interconnectivity and the patience required to allow the technology to grow.

the cloud, authorised parties can view the data collected on a web and mobile app dashboard. These sense-and-respond feedback mechanisms can be expanded to encompass humidity, air pressure, light and shocks.

This technology brings enhanced transparency, accuracy and responsiveness to the whole delivery cycle. Not to mention a good deal of comfort to all those involved.

Never break the chain: an exercise in preservation

With data being the entity that swirls around this core technology, all those with a vested interest will need to embrace cybersecurity as a safeguard against potential perpetrators.

Dashboard apps, like those built for Skypod, are configured to flash alerts, whether on breaches of temperature ranges, defined geofencing parameters, or light exposure data that signals any tampering during transportation. These can prompt appropriate action.

Serialisation – the practise of assigning unique, traceable numbers to individual saleable units – is leading the charge against counterfeiting, diversion and theft. Progressive track-and-trace systems are forming another safeguard. Advances in cryptography, where combinations of private and public keys protect data, are also building a robust security layer.

Similarly, with the rise of blockchain technology, first given the light of day by bitcoin, an open ledger stores blocks of data and preserves them in their original format with the entire decentralised user network shielding them from amendment, tampering or destruction.

In next-generation supply chain management, data preservation and product preservation will be one and the same, with an unbroken chain being the difference between usable and spoiled vaccines.

A proactive future: look forward now for structured plans

As IoT breaks into packaging logistics, a strong body of evidence is gathering in its favour. Drones armed with smart shippers are already proving invaluable in Vanuatu; vaccines for immunisation are being transported there by air. It therefore follows that countries like Indonesia, with 18,000 islands in its archipelago, could be prime beneficiaries. But uses are poised to go beyond emergency solutions, as they weave their way into mainstream digital strategy for worldwide supply chain operations. To date, solutions like data loggers have made information on shipments available, but only post-transit. Should a problem be identified, it can often take two to three weeks for assessments to be completed, before a shipment is released. With IoT allowing real-time assessments, the potential savings in time and costs are clear.

Carefully does it: technology that requires room to grow

However, these technological advances have further to go, and the 'where next?' is happening right now. Predictive analytics powered by artificial intelligence is helping the supply chain become increasingly proactive.

With the capacity to leverage multiple data assimilations, smart algorithms can detect patterns and make informed, accurate predictions. Weather forecasts can highlight risks before they are encountered, affording pallet preparation and advanced warehousing management. Transportation availability can be known ahead of time, allowing for more accurate future scheduling. Driving routes can be optimised to negotiate traffic. Drones or ships, for example, could sense their immediate environments, preventing delays. Orders can be anticipated.

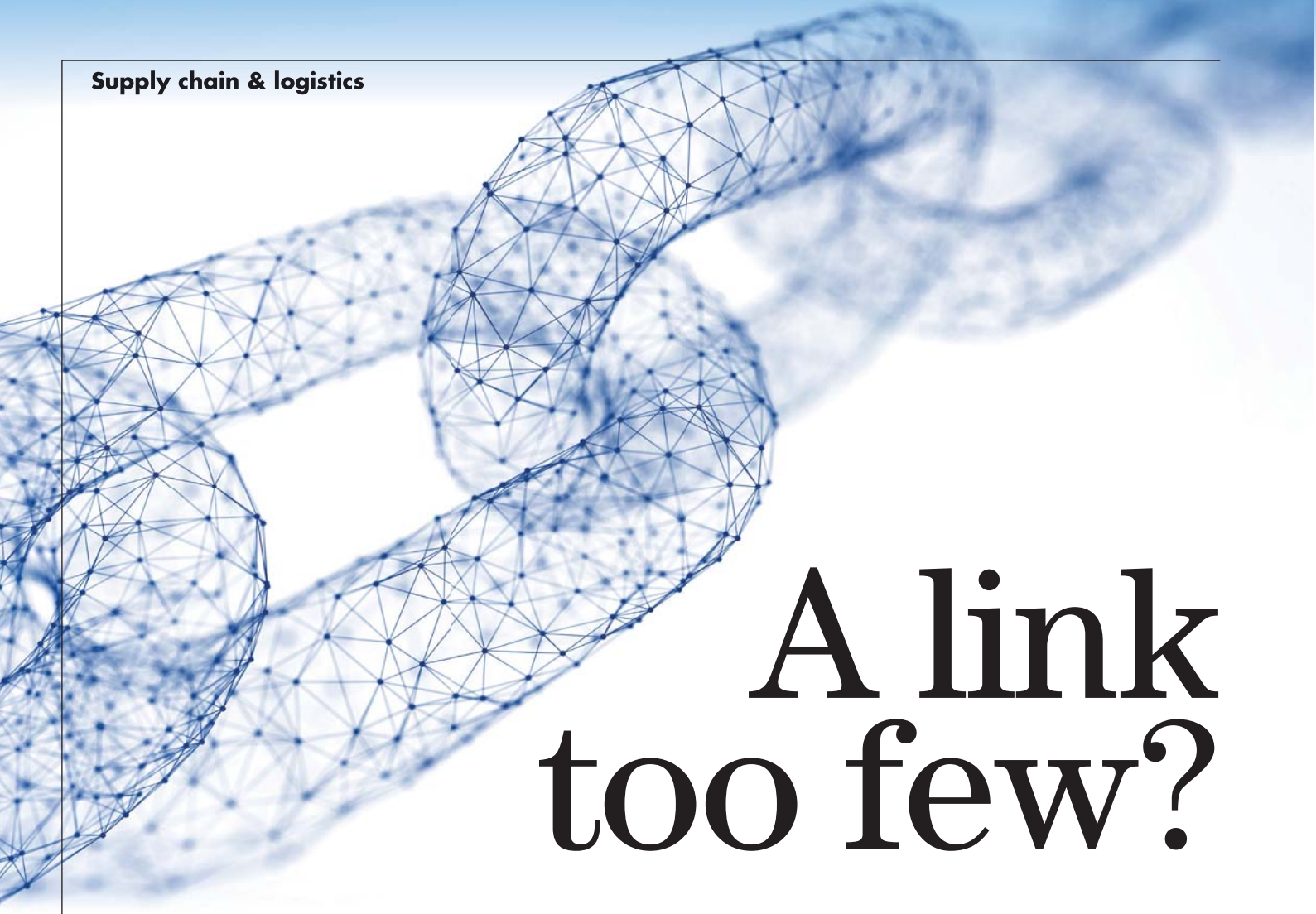
Laggards to leaders: a valuable investment

According to the 2018 Forbes report, "IoT marches into the enterprise, transformation follows quickly," companies that have embraced the IoT space are seven times more likely to see high growth rates, as productivity takes hold and new lines of business kick in. Additionally, more than three quarters of these companies have seen it as a precursor to increased revenue or profitability.

All the current indicators would suggest that the value of IoT to any company involved in the supply chain will be significant. This is one area where laggards might consider rallying to become leaders. ●

For further information

www.softboxsystems.com



A link too few?

It has been implemented in the supply chains and procurement processes of several industries from diamonds to produce. Now, with new electronic serialisation measures, analysts say the time is right for blockchain adoption in the pharmaceutical sector. Patrick Kingsland explores the benefits and risks with **Pasi Kemppainen**, management adviser, serialisation and traceability, at Santen Pharmaceutical.

Invented in 2008 by an unknown programmer using the pseudonym Satoshi Nakamoto, blockchain – a distributed ledger technology that underpins cryptocurrencies like bitcoin – was, for most part of the decade, a fringe experiment, popular among anti-state libertarians, tech insiders, and those looking to make a fast buck from something the law would most likely forbid.

But in the past few years that reputation has been changing at a dramatic pace. In 2017, the so-called 'great crypto bull run' saw the value of bitcoin – a currency that does not rely on any central authority – grow by more than 1,000%. Developers around the world quickly took note and despite a price crash in 2018 some of the world's biggest companies were soon showing serious interest.

Today, the multinational IT giant IBM is working with the US retail corporation Walmart to develop a blockchain solution capable of tracking food through its vast, global supply chain, in an effort to better regulate food safety. IBM has also launched a blockchain platform aimed at the financial services industry. To date nine financial services companies, including Barclays and Citi, have signed up to be involved in a proof of concept.

A report last January in MIT Technology Review claimed that 2019 will be the year that blockchain technology finally becomes normal. The technology will soon be so commonplace, the report added, that it will start to become mundane.

As blockchain enters the mainstream, many now say it could be used in the pharmaceutical industry to help companies increase security in their supply chains and allow for better tracking of drug products.

The conversation is being driven by new regulations from the European Medicines Agency (EMA) and the Federal Drug Administration (FDA), that are aimed at improving supply chain security and tackling the scourge of counterfeiting.

According to the World Health Organisation, one in ten medicines in poor countries are falsified, a problem that costs the lives of hundreds of thousands

of people every year. The problem also affects the developed world. Research by the Pharmaceutical Security Industry, a US-based non-profit organisation, suggests up to 19 million US citizens buy medicines from foreign online pharmacies and other unlicensed sources that may be unsafe.

Among other things the new regulations require manufacturers to create unique identifiers and anti-tamper devices for all of their pharmaceutical packages. This will allow drugs to be tracked more efficiently through the supply chain and could lay the groundwork for future blockchain systems.

While many remain sceptical of the technology, efforts to demonstrate its utility are already under way. In March, the logistics giant DHL announced it had partnered with management consultants Accenture to create one of the industry's first blockchain-based supply chain prototypes.

Since 2016, the Center for Supply Chain Studies, a non-profit organisation, has been conducting a research initiative on the use of blockchain in the pharmaceutical sector. The organisation says 45 companies are part of its core study team, and 150 companies belong to the associated interest group.

In a recent global survey conducted by Deloitte, 60% of respondents from the healthcare and life sciences industry said they are likely to lose competitive advantage if they do not invest in blockchain technology. Just three quarters of healthcare executives and 70% of life science executives described their understanding of blockchain as either excellent or expert.

"Blockchain is at an inflection point, with momentum shifting from 'blockchain tourism' and exploration to the building of practical business applications," said Deloitte.

Supply chains, unshackled

While it sounds complicated, blockchain is based on a relatively simple idea. A chain of blocks, each containing information such as a transaction or an agreement, are stored chronologically and across a network of computers. The chain is made available to anyone and once data is recorded inside it becomes very difficult to change or tamper with.

The security this system provides is why analysts says blockchain could make a major difference to pharmaceutical supply chains and prevent counterfeiting. As things stand it remains hard for pharmacists that distribute drugs to tell if products have been falsified without trawling through a large, cumbersome audit trail.

The trails are cumbersome because the pharmaceutical supply chain involves a number of different parties from manufacturers to wholesalers, suppliers to logistics companies. Each has their own responsibility to ensure the correct drugs are kept and stored in the correct way, be it temperature, humidity or simply stopping the item from getting into the wrong hands.

The complexity of this system means the different parties, "may not be able to offer complete visibility on the authenticity of the drug whilst ensuring quality has remained intact," said PricewaterhouseCoopers, a multinational professional services network, in a report titled 'How blockchain could strengthen the pharmaceutical supply chain'.

With blockchain technology, analysts say every stage of the supply chain – from creation to the end user – could be tracked in a seamless, accurate and secure way.

When a barcode is scanned it would be recorded on a blockchain ledger, creating a single audit trail that would be very difficult to tamper with. Sensors that measure temperature or humidity could also be recorded and added to the chain.

As the academic Don Tapscott has said in his book, *The Blockchain Revolution*, with such a system "you don't need intermediaries to ensure parties will act with integrity, because the very platform you're transacting on does that for you trust is not achieved by middlemen but by cryptography, collaboration and clever code."

Dreams versus reality

Of course, not everybody is convinced. Some analysts say the distributed, decentralised nature of blockchain technology poses more questions than it solves. Others say the technology remains too slow to be used on a large scale and consumes too much energy.

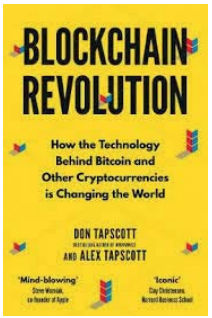
"Who can drug authorities go after if something happens with this blockchain network, if somebody misbehaves or it doesn't work as intended?"

In the pharmaceutical sector, while the idea may intrigue some drug manufacturers the vast majority of those actually promoting the technology appear to come from outside the industr – from consultants, from vendors and from technology enthusiasts."You have the industry view that is more realistic and focuses on how the technology fits the current landscape, ways of operating and legislation," says Pasi Kemppainen, management adviser, serialisation and traceability at Santen Pharmaceutical. "Then you have the more idealistic view that only applies if we had a perfect world. This is really what the problem is with blockchain. It is a fantastic theory and technology but then we

19 million

Number of US citizens who buy medicines online from overseas.

Pharmaceutical Security Industry



Blockchain Revolution **by Don Tapscott.**

look at the pharmaceutical industry – especially from the supply chain point of view – and it really doesn't solve the problems that the industry is having."

For Kemppainen, the cold, hard reality of the pharmaceutical sector is that it is a highly regulated industry. Introducing a new technology for serialisation and traceability therefore requires much more than just an underlying technology like blockchain. It instead requires compliance with regulators, validation of the technology and vendor, corporate integration with IT systems and supply chain partners, and far more to boot. As it stands, it is not clear blockchain is able to satisfy any of these rigorous requirements – particularly when it comes to compliance and validation. With an open network like blockchain it is the infrastructure and algorithms that have inherent control rather than any one corporate entity.

"Who can drug authorities go after if something happens with this blockchain network, if somebody misbehaves or it doesn't work as intended?" Kemppainen asks. "Who is actually responsible for the algorithms and if there are problems and those algorithms need to be changed who does it? Then who can validate the changes have been done correctly?"

The only way to create accountability, Kemppainen adds, is to instead run a private blockchain. "But then you need to trust that third party and you are back in the set up you would have with a particular company providing any other type of IT system of database services," he says.

Untested and unproven

While the immutability of blockchain is often heralded as one of its greatest assets, for pharmaceutical companies that need to change or correct the details of goods being manufactured and shipped, it could also pose serious problems.

"It happens on a daily basis," says Kemppainen. "It could be that a product is on the wrong truck or there were less products in a certain shipment than originally intended. There needs to be a possibility that you can change the data that you have already provided to your business partner. Immutability is great but here it could be a major disadvantage."

The transparent nature of blockchain could also be seen as business risk. In the pharmaceutical sector – as in many others – data is only exchanged between parties that have entered a contractual relationship. Two parties who share data on a particular shipment of goods, for example, will not want a third party involved.

"Blockchain is a fully transparent data exchange platform and that is not very realistic," says Kemppainen. "In many cases the transparency that it provides would actually be considered a disadvantage."

Kemppainen says these problems are amplified when you consider the amount of functioning technology that already exists for supply chain serialisation and traceability. Even regulatory bodies in Europe, the US, China, South Korea and further afield, now provide the kinds of services that blockchain is supposed to perform.

"There are already big infrastructures in place for providing the capabilities that blockchain, in an ideal world, is offering," says Kemppainen.

Blockchain is a network system of blocks containing specific information, available across a wider network.

The best solution

Of course, there are a great number of countries in places like South East Asia and Africa where there are no government-driven track-and-trace initiatives in place. In these less regulated markets, Kemppainen says blockchain could potentially become a useful platform for exchanging data between different stakeholders.

But even here he cautions that "blockchain would require all the pharmaceutical companies, wholesalers, hospitals and pharmacies to openly collaborate," – a tall order in emerging economies.

Back in the developed markets, pharmaceutical companies remain under significant pressure to meet new regulations and adapt to the healthcare needs of tomorrow. Experimenting with untested blockchain technology and lobbying regulators to change the law to enable it seems unlikely – at least for now.

"It is novel, it is untested and people don't really have any experience of working with it," Kemppainen says. "In short, they don't have a problem where blockchain would be the solution."

The compliance conundrum

For smaller pharma and their suppliers, meeting legal requirements has long been a significant challenge. GS1's **Geraldine Lissalde-Bonnet** and Centrient Pharmaceuticals' **Robert-Jan van der Horst** believe it to be a challenge that needs facing down, as Andrew Tunnicliffe explains.

For almost all of its existence, the entire pharmaceutical sector has had one enemy standing head and shoulders above the rest – counterfeiting. From pet care to over the counter medications, skin creams and ointments to some of the most important therapies available, counterfeiting has been attempted. Anti-counterfeiting legislation has been around almost as long, with each new iteration being more intelligent, and complex, than the last.

In 2013, industry commentators opined regulators were looking to usher in a new era, fundamentally changing the climate for pharmaceutical manufacturing and distribution compliance, with a raft of new legislation aimed at better securing the supply chain, ultimately closing avenues for exploitation. That legislation is still being implemented today.

Act of tenderness

Making better use of newer technologies, US and European regulations were drafted and implemented in 2013, staggering their roll-out over the following decade in order to let manufacturers have the time needed to implement them. The introduction of the US Drug Supply Chain Security Act (DSCSA) and track and trace via serialisation through the Falsified Medicines Directive (FMD), almost seemed as though they were set to work in conjunction, tying counterfeiters' hands.

"By allowing the use of global standards for product identification and data exchange, these regulations will enable increased automation in supply chain operations," comments GS1's director of public policy, Geraldine Lissalde-Bonnet.

She says the EU's FMD recent deadline for implementation, 9 February 2019, and the US DSCSA, along with other requirements and developments, such as in Russia or China have been a major focus for companies working on regulatory implementation of pharmaceuticals' traceability. It's a view supported by Robert-Jan van der Horst of Centrient Pharmaceuticals. "Centrient Pharmaceuticals has successfully implemented serialisation along with our partners, contract

2006

Year that the PSC was created.

manufacturing organisations (CMOs) and customers – those that hold our marketing authorisations. We are one of the few generic pharmaceutical companies that can say we were ready on time and in a compliant manner," he says. "To get there, however, was a major challenge in terms of effort, technical challenges and preparation time."

For the sector, anti-counterfeiting packaging has perhaps never been so important, leading to an increase in spend on ever-more innovative technologies. A recent market analysis report published by Persistence Market Research concluded anti-counterfeiting packaging was set to enjoy 'strapping growth', largely driven by the US and Europe. It added the rising number of counterfeit products, along with increasing consumer awareness and the tightening of government regulations were the leading driver for its growth. However, it warned, the high costs associated with track and trace, and a lack of awareness for product originality were 'expected to pose severe challenges to the growth of anti-counterfeiting packaging market'.

"For our business-to-business customers, it is essential that the active pharmaceutical ingredients (API) used in the medicines they sell to consumers can accurately and effectively be accounted for," says Van der Horst. "Importantly, achieving better traceability of pharmaceuticals is key to ensuring patients are less exposed to falsified, expired, recalled, or otherwise harmful pharmaceuticals," adds Lissalde-Bonnet. However, Van der Horst concedes, serialisation is a factor for companies looking to become active in the pharmaceutical market.

Up to the challenge

His views highlight the challenges smaller pharmaceutical companies face when trying to break into, or protect their position in, global and regional pharmaceutical markets. Lissalde-Bonnet explains, "The challenges are often related to the time frame for implementation as most of the requirements are to come into force during the same period, and due to the readiness for the industry, as not all the supply chain is able to implement."

The pharmaceutical sector is changing, perhaps even undergoing a quiet revolution, with an increase in the number of smaller biopharmaceutical companies active. As attention shifts towards more tailored therapies treating smaller patient populations, niche developers are entering the mix. The challenge is they do not necessarily have the capacity, capability and clout of their bigger brothers. This is driving the growth in contract development and manufacturing organisations, and ultimately the supply chain. For mid-sized companies like Centrient Pharmaceuticals, formally DSM Sinochem Pharmaceuticals, Van der Horst says one of the most important things is to share the desire to be fully compliant with serialisation laws with their B2B customers. "It is our best way to assist in the fight against counterfeit medications," he says. "We also actively encourage our generic pharmaceutical producing peers to join organisations such as the PSCI to ensure greater industry compliance." The not-for-profit Pharmaceutical Supply Chain Initiative (PSCI) was established in 2006 with a mission to "promote responsible practices that will continuously improve social, health, safety and environmentally sustainable outcomes for our supply chains". Since, it has developed the Pharmaceutical Industry Principles for Responsible Supply Chain Management, leading to the creation of a supplier audit collaboration programme and supplier capability building programme. Members are pharmaceutical and healthcare companies, including AstraZeneca, Biogen, Celgene, Lilly, Novartis and Sanofi.

Van der Horst warns some API manufacturers are not members of such initiatives, to their detriment, and those using their products and the industry. "Irresponsible manufacturers add to the risk of medication that is not properly produced," he says.

"The main challenge for SMEs in preventing counterfeits is often linked to compliance with requirements differing from one country to another," adds Lissalde-Bonnet. "In addition, regardless of whether some will have already met the required timelines, the most important challenge is that the requirements are not always as clear as they could be and this increases potential non-compliance, thus increasing the risk that falsification may be achieved more easily."

This way to global recognition

In 2012 McKinsey & Company published a report on global standards in healthcare, supported by GS1 highlighting the financial benefits to manufacturers. Savings were estimated at $43–62 million annually, representing around 1.6% of base revenue and 6–9% in earnings before taxes. These were calculated as coming from a reduction in inventory assets; inventory financing and holding cost; produce waste due to obsolescence; costs of recalls; and, most importantly, fewer counterfeit products.

However, as the McKinsey report acknowledges, getting to a position of being able to reduce costs, financially and ultimately in any damage to reputation, is a significant challenge, particularly if investment is difficult. "Indeed, in many instances significant investment will be needed in order to be able to meet the requirements that come with a comprehensive traceability system," says Lissalde-

Bonnet. "However, there are resulting business benefits to be seen, and many organisations are undertaking their implementations of traceability from a strategic perspective in order to achieve those benefits."

She adds that having a globally-defined regulatory framework for pharma traceability will assist in specifying the requirements as they move through adoption phases. "Using global standards will also enable pharmaceutical companies to improve their supply chain processes and to leverage interoperability while implementing one system of globally harmonised standards to address different traceability requirements."

The report also warned of the threat posed by a inaction due to the concerns of high costs and lack of awareness for product originality. However, Van der Horst agrees concerns over cost are far outweighed by the benefits compliance can offer. "Additional measures to ensure compliance certainly don't drive costs down. On the other hand, it is of great importance for Centrient Pharmaceuticals that our products are of the highest quality and fully compliant. Only with those as a given can we ask a fair price for our products from our customers."

The drive to ensure the pharma industry employs track-and-trace technologies has gained pace in the past decade. However, the issues isn't just one for pharmaceutical manufactures, its increasingly becoming a matter for the entire supply chain, including dispensers, repackagers and wholesale distributors too.

Technology holds the key

A recent call by the US Food and Drug Administration (FDA) served to highlight this. Later this year it will be launching a series of pilot projects aimed at further securing the prescription drug supply chain as part of the ongoing DSCSA roll-out, and introduction of drug tracing and verification system. "Under this programme, the FDA will work with stakeholders to establish one or more pilot projects to explore and evaluate methods to enhance the safety and security of the drug supply chain. This programme is open to supply chain stakeholders," the regulator said. The goal is to help leverage new technologies to support the development of interoperable electronic systems.

It has been suggested, and not denied, the FDA is actively considering blockchain among those new technologies. The technology, that allows the secure transmission and sharing of information, has been a topic of much discussion in recent years. Its benefits mean data is stored across a network, making it harder to locate and manipulate. It also means that data is easily verifiable.

However, unlike the US, EU regulators have dismissed its potential, favouring a more traditional centralised option, to the disappointment of Van der Horst. "Blockchain could have been an option as a platform for serialisation. However, the EU and the industry decided differently," he says. "We have now ended up with a landscape of several IT vendors, each of them with its own network."

He says such a system results in more challenges for the industry, made more acute thanks to differences in the interpretation of standards. He argues one standard, such as GS1, should be applied "a common standard for identification".

Asked how SME pharma companies and new entrants to the sector can best prepare themselves for new regulation in the distribution of their products, he believes, "It is important to select an ideal IT vendor and look for synergies within the current IT landscape. The more harmonised the IT landscape, the greater the integration benefits, with a tool close to ERP systems, and a seamless business process. In companies with a very scattered IT landscape, it might be more advisable to go for cloud solutions. But then some parts of the business processes need much more attention as the end-to-end process cannot be fully automated. Supply chain benefits will be much harder to obtain too."

"The main challenge for SMEs in preventing counterfeits is often linked to compliance with requirements differing from one country to another."

Geraldine Lissalde-Bonnet

He adds that February's implementation of the EU FMD, along with DSCSA in the US, shows that the ability to account for the complete production of medicines across the global supply chain is increasingly important. However, he warns we are likely not yet fully protected from the curse of the counterfeiter. "For sure, counterfeiting will find its way into the marketplace, but now with 2D barcode scanning at the point of decommissioning, the likelihood of detection of falsified medicines has increased. How great the challenges will be for the counterfeiter in the future is not yet clear."

It's clear that for smaller and mid-sized pharma, and their supply chain, being compliant is more than just knowing the law and meeting its requirements. Investment is a major issue. Whether technology can help reduce that burden remains the big question, but one thing is for sure, having your products replicated by a counterfeiter is likely far more costly. ●

OPTEL™

INTELLIGENT SUPPLY CHAIN®

Our ***true*** **end-to-end traceability solutions** bring visibility to your supply chain, from the **raw materials** to **the patient**.

VALUE BEYOND COMPLIANCE

Leverage rich serialization data to gain actionable insights into your supply chain to improve your daily business operations.

OPTEL: N°1
IN **TRACK-AND-TRACE**
SOLUTIONS

MANUFACTURERS | CPOs | CMOs | VIRTUAL MANUFACTURERS | PARALLEL IMPORTERS | WHOLESALERS | DISTRIBUTION CENTRES | 3PL

optelgroup.com/pharmaceutical

Build the future

OPTEL GROUP's serialisation and traceability solutions help you leverage your serialisation investment to increase visibility into your supply chain, while simultaneously improving day-to-day business operations.

New regulatory requirements have shifted the pharma industry's focus to finding compliance solutions, but there's a way to comply and improve business operations at the same time. Below are three tips for using serialisation to move beyond compliance and build a more intelligent supply chain.

Mine intelligence from your supply chain

When shopping for a suitable serialisation partner, do not be afraid to ask the hard questions, such as whether the platform can deliver business value beyond compliance. For those who choose the right platform, architecture and partner, the answer is yes. Both parties should aim to gain insights and not only connections. The right serialisation solution can capture rich supply chain data and translate it into valuable information that you can mine and leverage to optimise your business.

The desired integration standards must be based on GS1's EPCIS standards. Most out-of-the-box integrations do not leverage EPCIS, the standard in serialisation data exchange. This means possible disconnection from partner networks and loss of access to valuable serialisation data if the decision is made to switch CMO or 3PL partners. Make sure the potential partner supports EPCIS for all integrations.

Most out-of-the-box serialisation solutions limit which supply chain data can be collected. Ensure that any prospective partner's solution can meet the company reporting needs with regard to customisation.

The partner should also support insights into production capacity, paths and duration, diversion and supply chain anomalies. If the only reports provided are on basic compliance metrics, it is simply not enough.

The world's top brands use OPTEL's serialisation and traceability technologies to track millions of products around the globe, every day.

Require intuitive reporting for better business decision-making

Some serialisation vendors do not even offer reporting tools for basic compliance needs, leaving you to navigate and rely on third-party reporting tools. The right reporting, designed for the client, is key } to creating a more intelligent supply chain. Clients must demand the reports that improve your business. The right serialisation platform will come with built-in, advanced tools to report on regulatory compliance requirements as well as on the health of the supply chain. You need to integrate partner data into reports to enable end-to-end traceability, so you know where your products are and whether you have enough supply based on forecasts, current demand and historical trend analysis.

Focus on insights rather than simply connectivity

One of the most challenging elements of any serialisation project is managing integration points with all partners, such as CMOs, 3PL partners, customers and government agencies. Most companies have found that out-of-the-box integrations do not offer any benefit. In fact, they can expose a system to additional risk and hidden costs, as they often do not leverage the EPCIS standard for data exchange. Choose a serialisation software partner that uses standard messaging and transmission formats and provides the platform features that allow you to leverage your data to create a more intelligent supply chain:

- **Insightful:** OPTEL translates your data into actionable insights with customisable reports designed to drive informed decision-making.
- **Intuitive:** OPTEL's platform offers a user-friendly interface, intuitive features and flexible integration options.
- **Proven:** OPTEL is used by the world's top brands for serialisation and traceability software, which is used to track billions of events and millions of products every day in 120 countries and 18 languages.

OPTEL's serialisation and traceability software analytics help to create a smarter supply chain. ●

For further information
www.optelgroup.com

An application of impeccable form

PHOENIX group has launched Pharmondo, a new app-based patient support program for oncology patients, based in Germany. The innovative service is detailed here, with regard to the changing process, as well as the inimitable benefits.

Insufficient compliance or adherence can cause enormous costs within the healthcare system. In Germany, the estimated medical costs resulting from the lack of compliance in taking medicines are approximately €10 billion per annum. Consequently, they are within the cost expenditures for major widespread diseases, such as coronary heart disease or oncology.

For the best outcome

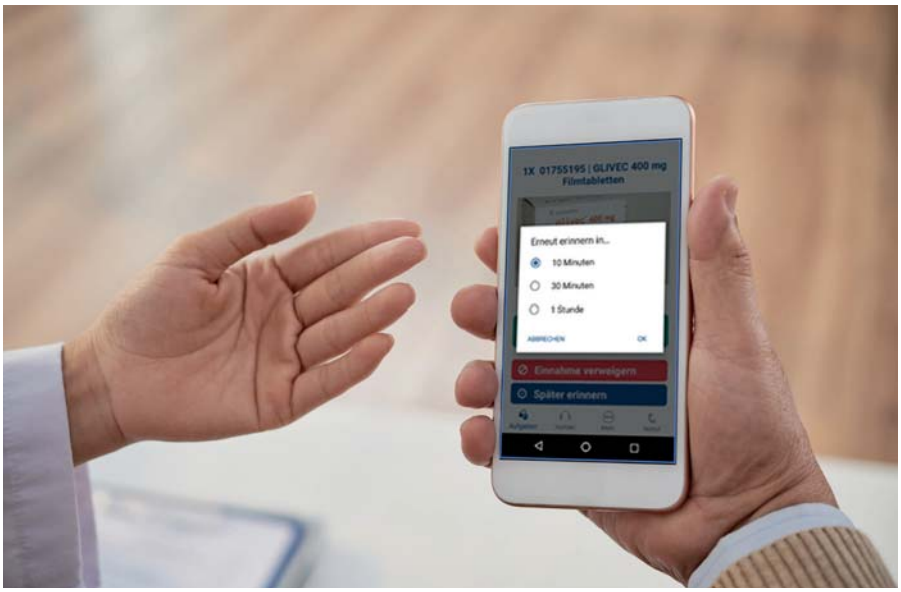
To obtain optimal treatment outcomes, such as cure or improvement in quality of life, treatment adherence is crucial, especially for oncology patients. However, many studies show that treatment adherence is still very low.

Therapy schemes often stipulate a slow increase of the required drug dose at the beginning of the therapy, until a tolerance threshold is reached. For the patients – especially those with a serious health condition – it is sometimes particularly difficult to follow the doctor's instructions.

The primary solution

To help patients stay on therapy, PHOENIX group has co-developed a patient support program that saves any therapy data and reminds the patients to take their medication. The program is marketed under the name Pharmondo, a cooperation between Virion and Oto-Care, in Munich.

Virion, a 100% subsidiary of PHOENIX group, is a specialised wholesaler with the main focus laid on orphan drugs and speciality medicines. As distinguished from many other medication apps, with its app, the doctor has the possibility to individually adapt any therapy for each patient and furthermore conduct therapy-accompanied surveys on the quality of life. Once the patient confirms the medication intake or answers a survey, the doctor gets notified about the completed task or the result of the survey.



The mobile app 'mara' helps patients to monitor their therapy.

The Pharmondo principle is based on four different modules:

- **mara:** medical adherence reporting assistant
- **otocare:** medication schedule
- **otocare:** healthcare terminal
- **PROTab:** Patient Reported Outcome monitoring.

Extrapolation of the core offers

The first module, mara, is an app that is provided to the patient on a separate smartphone. The app can be used with any medication plan. Therefore, no additional apps are necessary. The app helps the patient monitor his therapy, includes a medication intake reminder and enables the patient to monitor his side effects. The app directly connects the patient with the treating doctor and the responsible pharmacist, so that they always have an overview about the therapy progress and possible complications. Furthermore, a healthcare terminal was developed that enables the patient to directly scan prescriptions at the doctor's office and submit the order to their preferred pharmacy. This way, the patient does not have to come back to the pharmacy a second time if the medication is not in stock. The terminal also includes approximately 3,000 mail-order pharmacies that allow home delivery.

Transferable and compatible

With the comprehensive pharmondo-concept, PHOENIX group has succeeded in placing the patient at the centre of the therapy and in establishing a network channel for patient, doctor and pharmacist – entirely in the line with the company's much-lauded and value-adding PHOENIX All-in-One service. ●

For further information

www.phoenix-all-in-one.eu

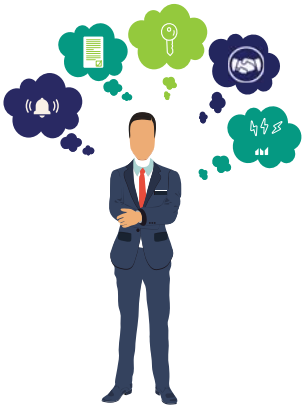
PHOENIX group

Our solutions for your challenges

PHOENIX All-in-One helps you reach your goals – Europe-wide

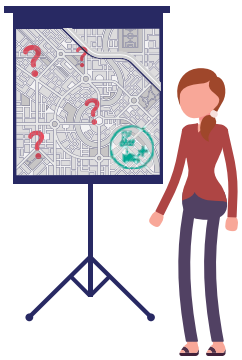
We help ...

... **Peter** to analyse the product performance for better business decisions.



... **Steve** to launch his new medicines in several European Markets.

... **Clara** to optimise the supply chain throughout Europe.



... **Mike** to organise Clinical Trials for his new medicine.

www.phoenix-all-in-one.eu

A practical guide

4Advice offer 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 consultantancy 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.

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

Today, the company he helped start is 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 improvement 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. ●

For further information

www.4advice.eu

A breath of fresh air

Transporting pharmaceutical products by air requires complex logistical processes, specific equipment, storage facilities and harmonised handling procedures to maintain shipment integrity. Despite the recent trend towards sea freight, the evolving technological landscape is changing the game. **Amy Shortman**, CEO of ASC Associates, speaks to Emma Green about both the challenges and opportunities for the industry.

The transition from air to ocean freight has been taking place over the past 10 years. Traditionally, many pharmaceutical products were sent by general air freight services. Unsurprisingly, this resulted in temperature excursions, an almost inevitability due to the complexity of air freight and the many handover points. A number of industry reports highlighted the lack of compliance occurring in these modes of transport, leading to widespread concerns about the quality of the supply chain and reflection on how methods could be improved. In addition to the compliance issues, companies have come under increasing pressures to cut costs, particularly in logistics.

Today it is no longer only specialist couriers that have extensive knowledge of temperature control within the supply chain. We now have third-party logistics (3PLs) and shippers who are well versed in good distribution practice (GDP). Although this is still trickling down to other stakeholders in the supply chain, compliance standards have been boosted within the industry. This has triggered a reconsideration of the value of air freight for transporting temperature-sensitive products, with more 3PLs now providing specialist services.

Amy Shortman, CEO of ASC Associates, has witnessed these trends in working within the industry for the past 25 years. Starting her career as a global specialist clinical trials logistics supplier, before establishing the UK and Irish operation for one of the world's leading active temperature control container organisations, she has worked within road, sea and air freight and thus has been able to gain a 360° perspective of logistics in the pharmaceutical supply chain. Looking at current industry practices, the rapid technological advances have opened up huge potential for optimising tracking shipments. "Historically, retrospective temperature data was used to prove that a shipment had been kept at a certain level," says Shortman. "We now have technology that can monitor that in real time and can highlight any temperature variations."

More than just providing information about temperature, recent developments have facilitated the ability to predict key issues along the supply chain. Although in their infancy, such technologies can provide valuable insights. "So if you imagine a temperature-controlled truck bringing in products, they can tap into the telematrix of that vehicle and bring that data in," explains Shortman. "Then once it goes into an air freight environment, it can also get information about issues like flight delays, civil unrest, strike action as well as temperature data of the actual product, as there are also monitors inside

the shipment." This data is valuable in enabling companies totake action quickly and prevent major issues from occurring. "By bringing this all together, what they're doing is real-time auditing of their supply chain and adopting a risk management approach to every single shipment," says Shortman. "I think these technologies are going to be massive in the future."

Not a novel idea

This is a novel trend, particularly for air freight, which has traditionally been seen as a 'black hole'. "This new technology allows for visibility of your freight, in any environment globally, knowing exactly where it is through GPS, the temperature it is, how it's being handled and having the ability to connect to various different companies," explains Shortman. "You might have 10 different airlines that you're using, with three different forwarders; you don't necessarily want to be going into each of their individual systems to get data, you want that to be proactively sent to you and then to be filtered through algorithms to give you what you need."

These technologies are also providing enhanced visibility of the supply chain that has historically never been possible. "Through smart technology, you can use tablets and phones via an app to take photographs and to upload live checklists, speak to a driver, talk to someone in a warehouse via a system so that all of that information is going up into a cloud and is available to anyone who needs to see that within the supply chain," says Shortman. "That is a real game-changer."

In addition to the rapidly developing technologies, personalised medicines are also driving change in the industry and causing companies to reassess the value of air freight for temperature-controlled products. "We're going to see a shift in the next 10 or 20 years with more personalised and highly complex medicines entering the market," explains Shortman. "Those will be more suited to air freight."

This includes products like CAR-T therapies, which are more time and temperature sensitive than other types of pharmaceuticals. "These will have more of a natural synergy to the speedier types of transportation because they have a more limited shelf life," says Shortman.

Personalised medicines also tend to be shipped in low volumes, another key plus for air freight. "Traditionally, ocean freight has taken large volume, low value," says Shortman. "There's a break-even point for most companies whereby if they have only a small number of pallets, it is more economical for them to use air freight for very low-volume, high-value products."

Hit the open road

Although these developments are new for air freight, they have been used successfully within road freight for a number of years. "We've seen the value in areas that are high risk within a road freight environment of having a system that not only tells you that somebody has stolen your load but as part of that escalation, will direct to law enforcement so that companies don't have to wait for someone to pick up the phone and say my load has got stolen," says Shortman. "Instead they can go into a system via an app, and track the load themselves."

These capabilities are especially beneficial for high-value pharmaceutical products, which can have dangerous consequences if they fall into the wrong hands. "We don't want products to be entering into either an illegal supply chain or to be taken outside of the temperature range and then put back into the supply chain and then to be put back into it," says Shortman. "It's really important for patient safety that we manage those issues as quickly as possible."

It all comes together

In order to optimise control of the supply chain, it is necessary to not only track products in air freight but all products, regardless of how they are being transported. Although there is a wealth of data available, there is currently a lack of tools that are able to amalgamate these disparate sources in a GDP compliant manner. "While you can access various bits of data, if you're managing logistics for a global pharmaceutical company, you would not have the time necessarily to view all of that," explains Shortman. "What you want to do is have a system that is bringing all of that together so you have one view of where all your shipments are globally irrespective of which airline, which forwarding company, whether they're being shipped by ocean or air and then to know whether there are any issues."

"Today it is no longer only specialist couriers that have extensive knowledge of temperature control within the supply chain."

Of course, in order for this data to be useful, it has to be actionable. "It's is brilliant that we're getting all of this data globally from various different sources," says Shortman. "We're seeing huge interest from shippers who don't want to be told about every bit of handling that goes wrong but instead to have a system that gives them an overview so they can monitor logistics companies to see how they're handling their freight from a performance point of view." This allows enhanced risk management but also for insurance premiums to be reduced. ▶

10

Number of years that it has taken to transition from air to ocean freight transportation in the pharmaceutical industry.

All aboard an effective measure

Making effective use of this wealth of information is not a technology issue. “When you talk about things like AI and technology, we have a generational skills gap of people who are now in senior positions that perhaps are not as au fait with technology as the younger generations,” says Shortman. “For example, 25 years ago, we did not have access to the internet to see whether our shipments had flown as booked, it would have been a manual process of phoning them up and giving an airway bill number.”

The speed of change is not likely to slow down any time soon and it is thus imperative that companies put themselves in the best possible position to take advantage of its capabilities. “It’s about investing in upskilling existing workers to become more aware of how technology can benefit their particular roles,” says Shortman. Although this is an effective long-term strategy, other approaches can help to save both time and money. “We’re certainly seeing more and more companies outsourcing to get immediate expertise,” says Shortman. “A lot of the time they don’t necessarily need to employ a full time person for that role.”

This isn’t about just about building competencies among select individuals. “I think that where we’re talking about things like AI, I feel that we have an obligation to make sure that we are upskilling the whole industry,” says Shortman. “The future changes are going to be quite profound, particularly within transport and logistics.”

However, this doesn’t mean that everyone needs to become experts in these technologies. “I have so many people coming to me saying that 'I need to understand everything about blockchain,'” says Shortman. “I don't think that everyone is going to have to become an expert to be able to operate it. It is just being aware of what it is and how it is going to help processes in the future.”

The drive to progress

Although traditionally conceptualised as being a barrier to innovation, Shortman believes that regulation has been a powerful force in bringing about positive change. “It has forced everyone, whether that’s air, sea or road, to up their game,” explains Shortman. “That only ever happens when it’s driven by the regulators and then is pushed down by the shippers to all of the supply chain partners.”

These developments have no doubt improved the supply chain for all stakeholders and thus should be welcomed by the industry. Despite the considerable effort involved in ensuring compliance, in the long run, the time and financial savings more than pay off. ●

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 pharmaceuticals 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 shipment, QEP accreditation provides the improvement of ramp-handling processes.

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

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 tarmacfor 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.

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

The company successfully maintains the recertification process that will be performed by IATA every three years. The process of CEIV Pharma-certification for 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.

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 keeping 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 used especially 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

FROM PARIS TO TORONTO IN TIME FOR ALLERGY SEASON.

At the core of our vast global network is a dedicated team making sure your pharma shipments are delivered quickly and safely. Be it allergy medication, vaccines or medical isotopes, our commitment is at the heart of every shipment.

Visit aircanadacargo.com today.

WE'LL FIND A WAY | AIR CANADA CARGO

Enhancement has lift-off

Air Canada Cargo kicked off 2019 by focusing on providing an enhanced product and service offering for pharmaceutical shipments. Here, these efforts are extrapolated on.

In February 2019, Air Canada Cargo announced the first of several key steps in its revitalised offering – a collaboration with GTA dnata. In effect since late February, this innovation at Toronto Pearson International Airport YYZ adds a state-of-the-art facility to the carrier's arsenal. Since then, all pharmaceutical shipments touching its global hub at YYZ are handled exclusively at the GTA dnata facility. GTA dnata is CEIV Pharma-certified for its handling processes and facility, which is fully equipped for handling temperature-sensitive shipments in varying environments and uses advanced monitoring technology.

Air Canada Cargo maintains hubs worldwide to support hundreds of pharmaceutical shipments.

The lion's share: consistent technology across the range

"This collaboration reflects Air Canada Cargo's commitment to fulfilling our customers' evolving needs for pharmaceutical shipments," says Vito Cerone, managing director, sales and commercial strategy for Air Canada Cargo.

The largest share of specialised products shipped with Air Canada Cargo are booked with one of its AC Cool Chain solutions. Air Canada Cargo's largest global hub feeds hundreds of flights; more pharmaceutical shipments flow through Toronto than anywhere else in the carrier's network.

"Adding a CEIV Pharma facility to our offering in Toronto made perfect sense," says Carolyn Van Vliet, manager, cargo products and business development. "It is a direct response to our customers' requests. For us, this was a turnkey solution that allowed us to respond quickly to a growing need."

The capacity to streamline future technology

In addition to participating in the IATA's Time & Temperature Working Group, to further strengthen its commitment to quality, Air Canada Cargo will soon begin its own path to IATA's CEIV Pharma programme.

"The system enhancements will ultimately align product specifications with market expectations, from the start of the booking process and throughout the shipment's journey to destination."

Carolyn Van Vliet, Air Canada Cargo

"We are invested in quality and engaged in contributing to the improvement and alignment of standards in the supply chain," says Van Vliet. "The CEIV Pharma programme is a logical next step, in the revitalisation of our AC Cool Chain family. Air Canada Cargo is making simple enhancements to its systems that will help streamline processes and render the offering more precise. These system enhancements will ultimately align product specifications with market expectations, from the start of the booking process and throughout the shipment's journey to its destination."

Technology and infrastructure investments are planned for the Toronto hub, as well as for other Canadian hubs (Montreal, Calgary and Vancouver), its US hub in Chicago, its London hub and Frankfurt station.

The whole wide world

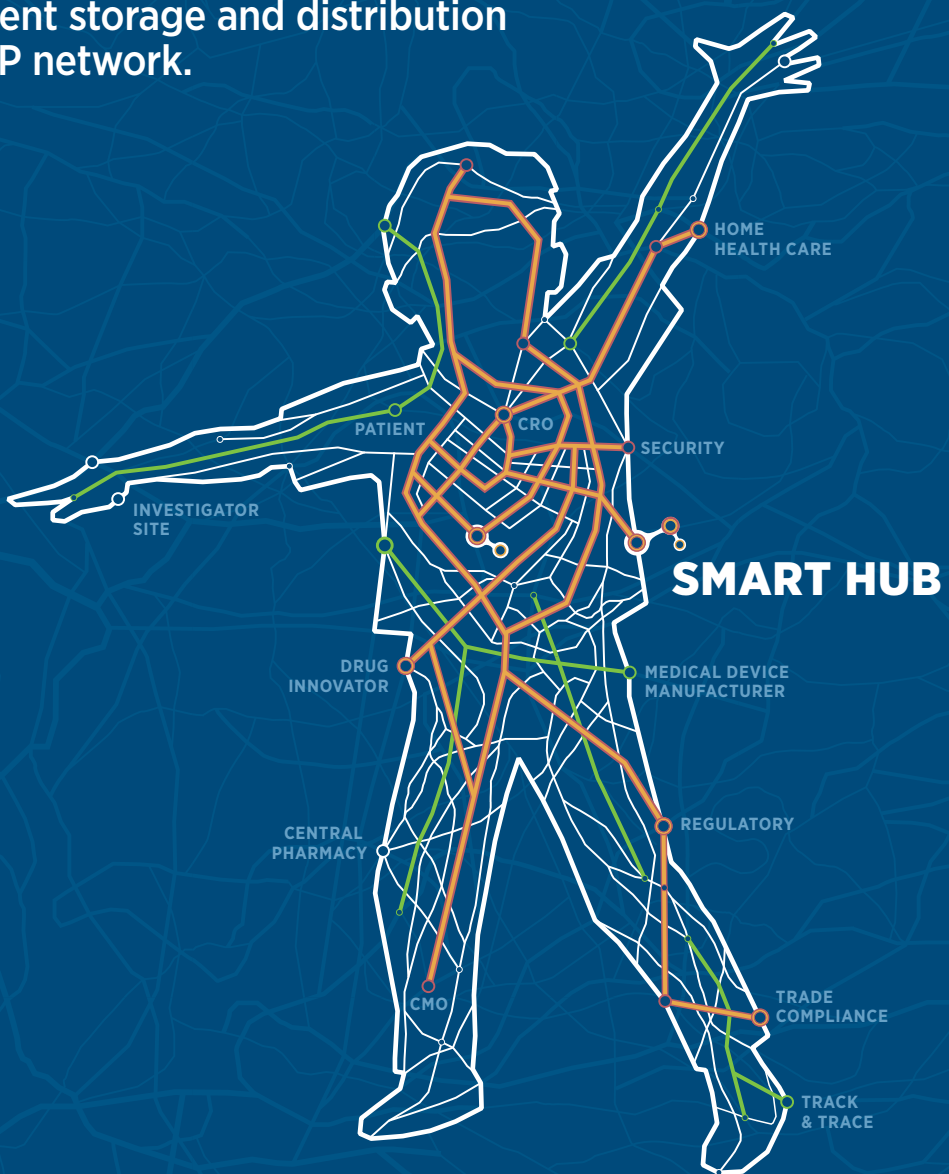
While the Toronto hub handles the largest volume of pharma shipments in Air Canada Cargo's network, including import, export and shipments in transit, it expertly transports pharmaceutical shipment to over 140 locations around the world. The carrier's ability to transit shipments via Canada provides quick options for international routings; for example, Melbourne to Seattle via Vancouver, or Brussels to Brazil via Montreal, with the new route to São Paulo starting in December 2019. ●

For further information

www.aircanadacargo.com

SMARTER HUBS. FLEXIBLE CLINICAL TRIAL LOGISTICS.

An intelligent storage and distribution global GMP network.



- Best-in-class quality systems, including global GDP compliance
- Every transport option, offering optimum efficiency and flexibility
- Leading-edge technology with end-to-end supply chain visibility
- Dedicated team of project managers around the world
- Patient-centric services support the development of personalized therapies

YOUR SINGLE SOLUTION FOR COMPLETE CLINICAL SUPPLY CHAIN ASSURANCE.

EXPERT@MARKEN.COM | WWW.MARKEN.COM

MARKEN
a UPS Company

Hybrid value

Traditional trial strategies often bring challenges to patient recruitment and retention. Sponsors are eagerly embracing the value that hybrid and siteless trials offer, and are exploring how logistics and supply chain experts like **Marken** can work closely with them and their patients through these types of trials.

Virtual and hybrid trials using a direct-to-patient (DTP) approach can make conducting clinical trials potentially more cost-effective. Patient centricity remains the primary driver of adoption of virtual/hybrid clinical trials, with stakeholders identifying improved patient retention (38%), the ability to reach dispersed populations (19%) and improved communication (17%) as the top three reasons for adopting DTP trials models, according to a survey conducted by Arena International Research. The growth of DTP and direct-from-patient (DFP) supply chain services in recent years has been in response to the need for minimal disruption to the patient's lifestyle while increasing their willingness to participate in a clinical trial.

Patient behaviour, expectations and technology are driving the strong interest in virtual trials. Streamlining logistics, the strategic involvement of supply chain partners in the protocol design, and simplified patient-centric services, form the new model for planning a successful clinical trial. Critical questions need to be addressed when considering adding a DTP protocol to a trial, such as how can all partners involved effectively coordinate the different parties connected to the patient to ensure patient data protection and privacy is maintained throughout the study across suppliers?

Always plan ahead

Sponsors need to understand the common regulatory challenges associated with home care, and DTP and DFP strategies. By exploring the set-up process for a successful trial and to avoid risk, critical points in operationalising home care and the last mile of the supply chain need to be addressed. Assess each protocol to verify which are most appropriate for DTP and DFP and home healthcare, and review the types of procedures commonly conducted in home care. Patient data protection and privacy can become a potential pitfall if not carefully secured with an experienced provider.

Marken continues to lead the industry in DTP and DFP supply chain solutions to meet the growing demand from the clinical trial industry.

Marken has demonstrated its ability to effectively manage drug product delivery to and biological sample pickup from patient homes, having adapted systems and processes to be compliant with patient privacy regulations. As the changes continue to evolve, the majority of clinical studies may be conducted with a DTP, DFP and home healthcare service component. As the clinical trial industry moves towards more personalised treatments, Marken services continue to expand for these more complex and specialised trials. With quality guaranteed through full temperature monitoring from pickup to delivery, Marken offers DTP and DFP services in more than 51 countries.

Express delivery

Marken worked closely with UPS to develop a service to allow nurses to drop off clinical trial samples at The UPS Store locations within the US. This unique service provides patients and nurses greater flexibility for home care during clinical trials. Nurses drop off blinded shipments at The UPS Store after sample collection at patient homes. All the store locations have the capability to handle UN3373 and UN1845, as well as pre-packed, prepaid shipments at all temperature ranges, including ambient, refrigerated and frozen samples. Marken manages the booking of shipments to ensure protocol compliance, patient data blinding and data encryption.

Patient-centric services

Marken's DTP clinical drug delivery and DFP sample pickup, combined with home healthcare (HHC) services by a global network of licensed providers, facilitates patient-centric trials. Next-generation, patient-specific treatments and precision medicines are becoming a part of more and more clinical trials, with DTP services offered as an option in many trials occurring worldwide. These new models expedite investigating drugs and supporting populations that were previously unfeasible, but they impose new demands on the logistics of the underlying supply chains.

DTP models present unique challenges associated with temperature control, requiring that drivers, nurses and patients take responsibility for maintaining the cold chain and reporting any excursions. Tracking the chain of custody for trial kits and ensuring patient data blinding – as mandated by the Health Insurance Portability and Accountability Act (of the US) and the General Data Protections Regulation (in the EU) – are further logistical challenges associated with DTP clinical trials that require protocols and speciality courier training to protect patient confidentiality and maintain blinding. To truly facilitate such complex clinical trials, pharma companies and CROs must partner with supply chain organisations that manage networks that adaptive solutions.

By using Marken's home healthcare service in combination with DTP/DFP services, sponsors can benefit from increased recruitment and retention rates as well as driving down overall development cycles and project costs. A dedicated home healthcare programme makes participation in a clinical trial as easy as possible for patients. With this global network of select providers allows Marken to offer the skilled services required under protocol.

By partnering with Marken, its clients benefit from an experienced provider offering a single integrated solution for every clinical trial. Expect more from your supply chain partner. ●

For further information

www.marken.com

Do 1000+ tests. Use simulation.

We are thermal simulation experts, providing you with simulation solutions tailored to the field of Temperature Controlled Logistics. Use our software packages to get quick and accurate answers to pressing questions at low costs.

Thermal Packaging

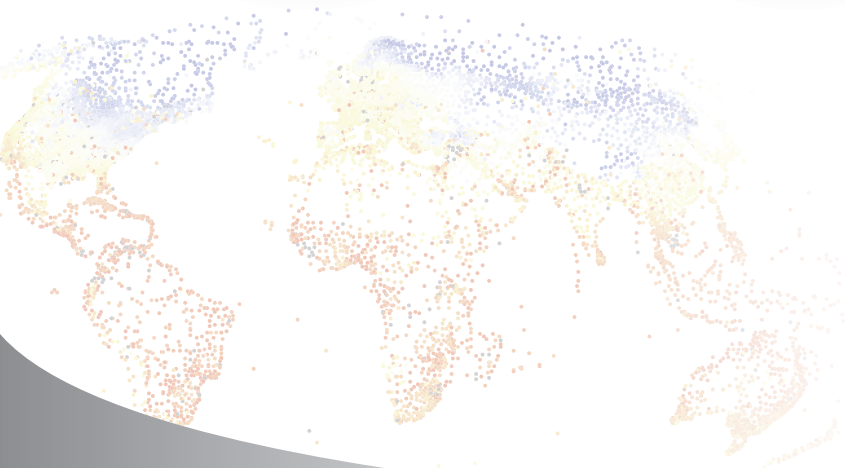
Build models of your packaging solutions and analyse their thermal performance.

Temperature Profiles

Get access to more than 20'000 weather stations worldwide and download historical and forecast temperature data of your distribution lanes.

Lane Risk

Predict the risk of thermal excursions for your shippers and products on your specific lanes.



SmartCAE Stefan Braun
Am Mitterfeld 3
81829 Munich • Germany

P +49 (0)89 45108878-10
stefan.braun@smartcae.de

SmartCAE

www.smartcae.de

Weather the storm

Global pharmaceutical supply chains are weak; there are many manufacturing issues and a lack of incentives to continue to produce less profitable but necessary medicines. Allie Nawrat explores how we can ensure that global supply chains are prepared to survive the next pandemic, natural disaster or trade war.

Medication shortages are worryingly commonplace worldwide. The US Food and Drug Administration (FDA) keeps a list of approved medicines in the US that are short supply; at the time of writing there were 105 drugs currently in shortage. This is cause for concern, because roughly 80% of active pharmaceutical ingredients (APIs) for US drugs are made outside the country.

However, the not-for-profit Access to Medicine Foundation focuses on the impact of drug shortages on low and middle income countries.

There are some high profile examples of shortages, such as Mylan's epinephrine auto-injector EpiPen, but it is common for drugs indicated for serious medical problems to be in short supply, antibiotics being a prominent example.

These shortages have led to questions about whether global supply chain share up to the task of tackling the next major disruption, whether it is a pandemic, natural disaster or trade war.

Pandemics can rapidly become global crises even if they only exist in select countries, because if that

country provides certain drugs across the world, it may choose to stockpile instead of export to help combat the epidemic. This in turn leads to shortages of that drug elsewhere.

Fiona Barry, associate editor at GlobalData's PharmSource, believes, "trade problems look more likely to cause major problems to drug supply chains than natural disasters." This has become a particular issue in light of the impact that the 2017 hurricane season had on the US territory of Puerto Rico. Hurricane Maria completely destroyed the island's electrical grid, meaning that several plants, such as those owned by Baxter International necessary to produce bagged saline, became inoperable.

What causes global drug shortages?

In its recent report, 'Shortages , stockouts and scarcity: the issues facing the security of antibiotic supply and the role for pharmaceutical companies', the Access to Medicine Foundation focused on the challenges facing the global supply of antibiotics.

It identified three underlying causes of antibiotic shortages: a small number of suppliers, a lack of interest in investment in antibiotic R&D and complex supply chains that have little visibility or any discernable accountability.

The small number of competitors at each stage of the supply chains means that failures or market exit from a single component can cause the entire chain to collapse.

"By far the largest shortage is manufacturing problems," Barry notes. "According to the US FDA, problems with raw materials, quality issues during production, and lack of facility capacity are the major factors." Mylan has repeatedly attributed its EpiPen shortages to production and manufacturing issues.

The International Society of Pharmaceutical Engineering (IPSE) and Pew Charitable Trusts conducted a survey in which they also identified manufacturing and product compliance issues as central causes of drug shortages.

The Access to Medicine Foundation's report found that the number of companies producing APIs in antibiotics is falling, which makes it increasingly hard for the industry as a whole to respond to surges in demand. For penicillin, which is in short supply in 39 countries worldwide, only four manufacturers globally make the APIs. Barry notes how the complexity of pharmaceutical supply chains creates vulnerability. She says: "Often, a drug's active pharmaceutical ingredient will be made by one CMO, and it will be turned into its finished dosage form at a second CMO. It could even be packaged by a third company."

Profits and patients

The Access to Medicine Foundation's study found that pharmaceutical companies are often reluctant to create new antibiotics because these

offer slimmer margins than medicines for indications such as cancer or cardiovascular conditions.

This is coupled with the fact that the antibiotics market is strictly regulated and some governments put pressure on companies to keep prices low because of the large number of patients reliant on these types of drugs.

The IPSE and Pew Charitable trust's survey found that company decision makers feel that market withdrawals are due to a need to focus on the most profitable projects. Companies also reported that a lack of incentives to remain in the space meant they couldn't resolve shortages or invest in building systems that could prevent them in the future.

Because of concerns about anti-microbial resistance, according to the Access to Medicine Foundation, when a new product enters the market, it will be used sparingly, meaning it is practically impossible for the antibiotic to gain the high sales volumes needed for companies to justify research and development.

European Association of Hospital Pharmacists (EAHP) president Petr Horák identifies the "unintended impacts of pricing and tendering policies" as one of the main causes of shortages.

The steps to prevent disruption

The Access to Medicine Foundation argues that solving drug shortages will only come from the combined efforts of governments, regulators and the pharmaceutical industry; however, the bulk of the work will need to come from government supported by international initiatives. Pew Charitable Trust' director of public health Elizabeth Jungman said in her company's report with the IPSE, "Drug shortages could be reduced with relationships between a manufacturer, a provider, and regulators." Barry discusses the work the FDA and European Medicines Agency (EMA) has done in this area, saying: "The FDA is also exploring incentives to encourage expansion of manufacturing capacity and enhanced quality, and consider developing a list of essential drugs for which it is critical to ensure an uninterrupted drug supply.

"It's also looking into financial incentives to make sure reimbursement policies aren't making it unprofitable to manufacture certain drugs that are more likely to go into shortage.

"Similarly, the EMA has said it is encouraging more collaboration between EU countries and pharma companies to prevent and manage any plausible disruptions.

"Also, mandatory serialisation of all medicine packages in the EU will come into effect in February 2019," she explains.

An issue of national security

The American Medical Association (AMA) has called on the Department of Health and Human Services to regard drug shortages as a national security issue, as well as echoing calls for industry and government collaboration to establish contingency plans in case of natural disasters.

The EAHP notes that drug manufacturers and wholesalers can help to mitigate the damage to the supply chain from drug shortages by giving adequate notice of manufacturing problems, which includes details about the shortage, such as how long it may last and specific products likely to be affected.

The FDA requires companies under its jurisdiction to do this, but is looking at ways to make this as easy for industry as possible.

"FDA Commissioner Scott Gottlieb has publicly supported the development of new production technologies such as continuous manufacturing to help ease shortages," says Barry. "Continuous manufacturing is less prone to the shortcomings that trigger many drug shortages, as it uses fewer steps and centralises the work, so problems can be identified quickly."

A further option is to resolve funding issues by producing a "'different financial model, or more government grants, to incentivise companies to develop these products'", according to Barry.

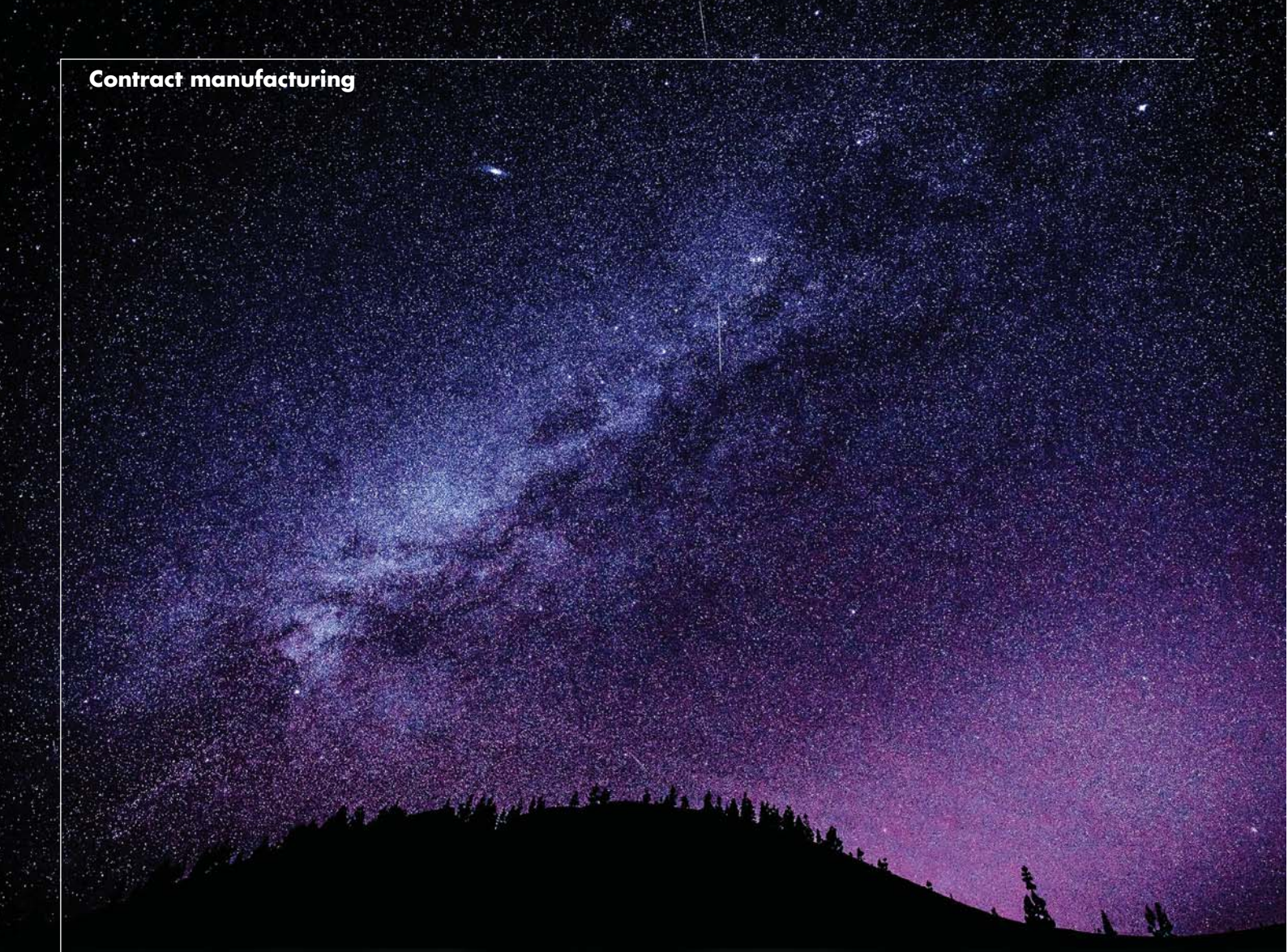
She believes this would help to deal with complaints from industry, and that "developing and manufacturing vaccines or antibiotics in preparation for these outbreaks isn't always profitable, because sometimes they're not used". ●

The pharma industry in Puerto Rico

Puerto Rico, often thought of as a holiday destination, is one of the globe's most vibrant hubs of manufacturing. The island became a popular destination for pharma companies after 1976, when the US Congress passed a tax code, Section 936, to make it more attractive for businesses. The law exempted companies from paying corporate taxes on profits made in the country, and was enacted to help bolster the island's sputtering economy.

Companies subsequently flocked to Puerto Rico to set up shop, including most of the biggest players: Pfizer, Bristol-Myers Squibb, Merck, Mylan, Eli Lilly and Company, among others. Amgen built its flagship site in Puerto Rico, which is also the biggest pharma facility on the island. About 90% of the company's products now pass through the 1.7 million square feet manufacturing complex, with about 2,000 employees. Puerto Rico became the go-to place to make high-profit blockbuster drugs.

In 1996, Congress decided to phase out the law over the next decade as the Puerto Rican government struggled to pay for public services and heavily borrowed to cover its growing deficit. Although the pharma industry was affected, with some jobs being lost and but many cuts were also related to mergers, and increased efficiencies brought on by technological advances like automation. Today, manufacturing still accounts for one-third of the island's GDP, of which the pharma industry occupies the largest percentage.



Keep it clustered

The industry faces a number of barriers in terms of pricing, as well as reimbursement, continued patent expirations and challenging market dynamics. In response to these, biotech clusters have become an increasingly important part of research and development strategies. Louise Thomas explores the factors that have led to the rise of these hubs and what they offer for the industry.

Traditionally, manufacturers have carried drug development projects from cradle to grave on their own research premises, away from the prying eyes of the rest of the world. However, this paradigm is rapidly changing, with companies responding to increasing industry pressures by engaging in greater amounts of collaboration and use of external resources.

However, these efforts are being concentrated in fewer places. The dominant industry model of large, diversified organisations with multiple hubs is being rejected in favour of a learner approach with an increased focus within key biotech clusters, and a particular focus on gaining revenue from speciality products, biologics and emerging markets.

Time and tide

Ajay Gautam and Xiaogang Pan from the IMED biotech units at AstraZeneca have identified four key trends, which have characterised the industry shift over the past 20 years and resulted in the growth of biotech clusters. These are massive to lean, primary

Figure 1. Distribution of global pharmaceutical sales across different regions (±1%)

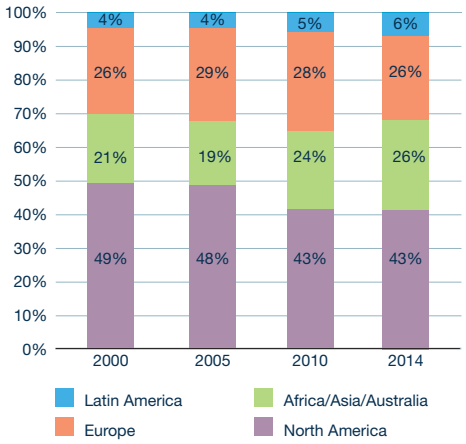


Figure 2. Average revenue (%) ex-US, EU and Japan, big-pharma cohort

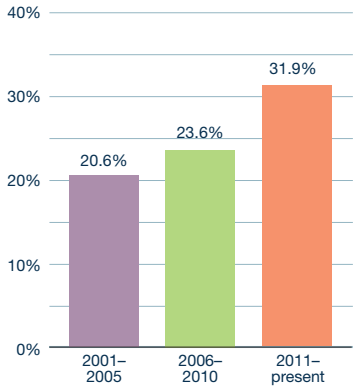
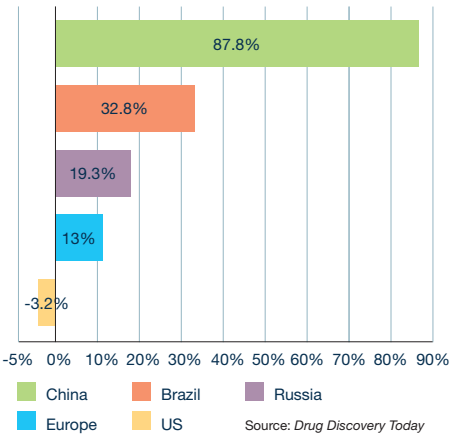


Figure 3. Average sales growth rate for 2010–14 period, big-pharma cohort



to speciality, West to East and hubs to hotspots models.

Massive to lean, the move from a 'bigger is better' towards a 'leaner and focused' model, was prevalent from around 1995 to 2005. This involved significant merger and acquisition activity, such as that between Astra and Zeneca, Ciba-Geigy and Sandoz, Pfizer and Warner Lambert, Sanofi and Aventis as well as Glaxo and SmithKline. This approach resulted in bloated operations worldwide, including big research and development hubs, huge numbers of sales reps, multiple manufacturing sites and matrixed governance layers. These challenges were exacerbated by a lack of cultural integration of the merged companies.

Since the late 2000s, the industry has transitioned towards a 'leaner and focused' model by reducing investment in non-core assets and instead emphasising their areas of strength. For example, Abbott split into two parts. AstraZeneca narrowed its efforts onto three core areas: oncology, cardiovascular-metabolism and respiratory, inflammation and autoimmune disease and subsequently reducing investment in other aspects. Bristol Myers-Squibb made the most dramatic changes, becoming a speciality company in oncology, cardiology and virology.

Acquisitions did occur during this period, however, these were largely strategic attempts to build complimentary capabilities, rather than being driven by a desire to become larger. For example, Pfizer's acquisition of Wyeth for biologics and Hospira for biosimilars.

This time, its personal

The 1995–2005 period was characterised by 'blockbuster' drugs. Many of the biggest sellers in the industry were released during this time and tended to be primary care, small-molecule therapies. At the time, these provided around 80% of the revenue for most big pharma portfolios. Since 2005, however, the industry has shifted away from these medicines towards speciality products focusing on unmet patient needs. This move was driven by several factors, including an improved understanding of the underlying disease biology, science and technology innovation, increased demand for personalised medicines and companion diagnostics, a favourable regulatory framework as well as pricing and reimbursement.

"Since the late 2000s, the industry has transitioned towards a 'leaner and focused' model by reducing investment in non-core assets and instead emphasising their areas of strength."

The biologics market was largely overlooked prior to this period but caught up in areas such as antibody, protein and cell therapies. This was achieved through targeted acquisitions; for example, Roche-Genentech, Sanofi-Genzyme and Lilly-ImClone. By 2015, this activity had started to pay off, with most companies now having a more balanced split between speciality and primary care. Although some companies have seen a drop in sales of speciality drugs over the past five years or so, this was primarily the result of expired patents of their top sellers.

The place to be

The US and Europe were the leading major markets for the industry between 1995 and 2005. However, since then emerging markets such Asia, Latin America, Russia, the Middle East and Africa have

heavily contributed to revenue growth. In 2014, for example, AstraZeneca sales from these markets accounted for around $6 billion in revenue, around $10 billion for GSK and $14 billion for Sanofi.

Not all companies made this same West to East transition during this period. Those with a heavier biologics focus such as Roche, JNJ and Amgen did not witness the same growth in revenue within these emerging markets because they did not face as many patient expirations in the US and Europe as their counterparts with primary-care-focused portfolios.

Aside from commercial growth, these areas have seen a large increase in innovation capabilities over the past decade, particularly countries such as China. As one of the world's top pharmaceutical markets, the country is rapidly becoming a global hotspot. Most pharmaceutical companies, including Novartis, Roche and Sanofi have established research units there.

The heat is on

The wave of large acquisitions in the early 1990s was triggered by declining research and development productivity. A consequence of this activity was the creation of multiple research hubs worldwide. For example, Pfizer's units in the UK and US; AstraZeneca's in Sweden, the US, Canada and the UK, and Roche's in the US and Switzerland. These created research silos that generated high-throughput technologies to address key scientific challenges, a 'more shots on goals' strategy. In contrast, the past decade was characterised by a desire to locate within bioscience hotspots such as those in the US and Shanghai. This enabled industry scientists to work with external researchers and clinicians to enhance their drug pipeline. A much more open and collaborative approach was thus created, in contrast with the prior hubs model.

Some pharmaceutical companies began to completely embed themselves within biotech clusters. Novartis was a particular pioneer in this area, relocating its research headquarters to Cambridge, Massachusetts, in the early 2000s, with several other companies following in their footsteps. Roche closed its site in New Jersey and moved to New York City, and AstraZeneca moved its research headquarters to Cambridge from Alderly Park.

Although large hubs are still in existence, the trend towards more focused hotspots has dominated the industry in recent years. This has also resulted in increasing use of CMOs and CROs for strategic drug alliances. The activity has provided the opportunity for large research organisations to work with both academic institutions and biotechs. Such efforts have been a huge paradigm shift for the industry but has resulted in the creation of a large number of new and cost-effective drugs reaching the market.

That could be arranged

The conventional approach of patent management by specialist IP departments means that questions of ownership are straightforward. Working with third parties in these biotech hubs invariably leads to more complex and challenging intellectual property issues than would arise within in-house research programmes.

Comprehensive arrangements need to be negotiated to ensure that the requirements of all parties are met, and due diligence is required to establish the ownership and extent of protection before any deals are made. Legal agreements incorporating these positions need to be carefully crafted, as disputes over ambiguous wording are common. Ownership rights between all stakeholders must be established at an early stage to ensure that outputs from these clusters are effective.

This new way of working demands a more flexible and creative approach than has previously been required, both in terms of the drug development process itself and negotiating the complex legal issues surrounding this activity. Given the benefits already being experienced through the work within biotech clusters, these are likely to continue to be areas of focus. Despite the challenges, these are invariably outweighed by the opportunities in terms of boosting research and development productivity and reducing costs. ●

A focus on China

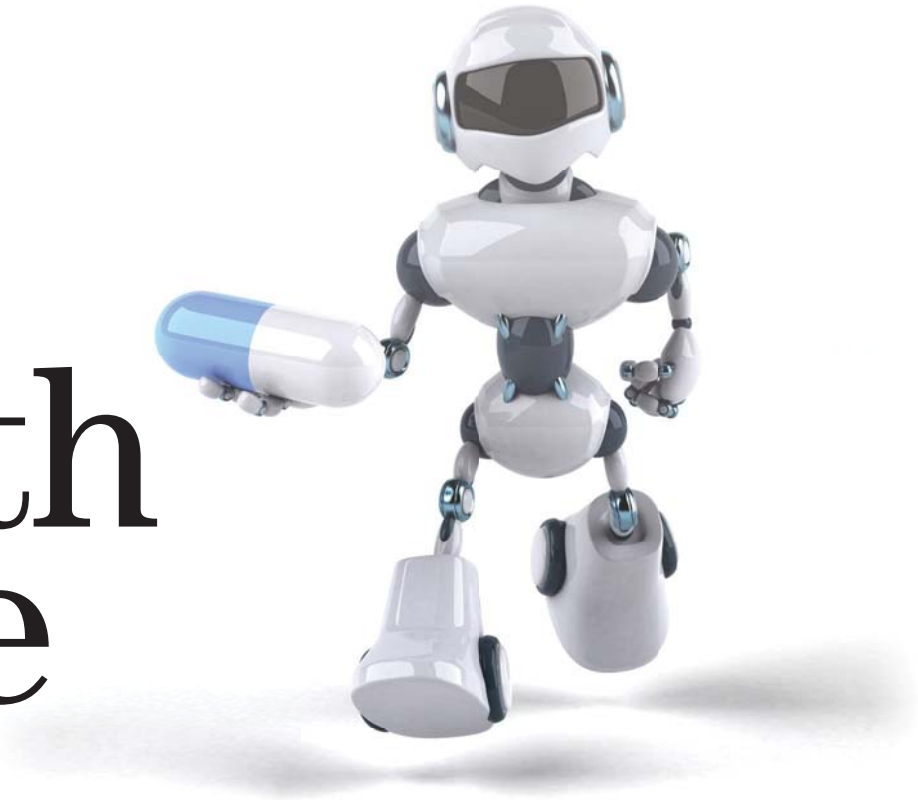
There are a number of drivers of research and development activity in China, most of which is concentrated within biotech clusters. The first of these is the outsourcing needs of pharmaceutical and biotech companies to boost productivity, manage costs and create operational flexibilities. Increasing complexity of biological targets, portfolio prioritisation as well as budget constraints have also resulted in the outsourcing of certain discovery activities on non-core aspects.

Outsourcing has taken place across a range of drug discovery areas, from chemical synthesis to target identification and validation to biological testing. CROs in China have also built a number of technology platforms for genomics and proteomics research, high-throughput screening platforms as well as mature and binding assays. For these reasons, China has become a preferred location for its end-to-end technological capabilities.

Government policy and initiatives have also heavily contributed to this activity. Biotech has been identified as a key priority for funding, which included significant investment into clusters. These are particularly effective because of the close proximity of pharmaceutical and biotech companies, helping to facilitate collaboration. CROs benefit by being able to access key features, such as the infrastructure, incubators, public research and development facilities within the cluster. This is in addition to the subsidies, permits, import pools, talent pool and financing available.

Research and development challenges are likely to continue to drive increased outsourcing, with China as the key area for such work. Future areas of growth in China include the niche services segment, such as target identification, hit generation and optimisation studies in addition to targeted animal model studies. Biologics are also likely to drive activity in the country, with CROs already building capabilities within this area.

The fourth wave



A lot has been written on big data and industry 4.0, and how they are rapidly transforming a number of different industries. However, not so much attention has been paid to how industry 4.0 solutions can be applied to pharmaceutical manufacturing. Emma Green speaks to **Karen Taylor**, director of the Centre for Health Solutions at Deloitte, about how these technologies can improve productivity, while minimising waste and risks.

We are all aware of the rapid pace of change across multiple industries as a result of significant technological advances and the reduced costs of using them. These trends are distinct from merely a greater level of process automation driven by developments in electronics and information technology since the 1970s. The greater adoption of industry 4.0 is now paving the way for disruptive approaches in a number of areas, including pharmaceutical manufacturing.

It's important to note that these technologies are not new. "What's changed is the cost and the fact that the connectivity and miniaturisation and computer speeds and the infrastructure has all changed to make it a reality to apply it at scale," says Karen Taylor, director of the Centre for Health Solutions at Deloitte. These trends are in line with Moore's Law, which predicts that the capacity of microchips, bandwidth and computers doubles every 18 months, representing exponential growth.

Between robots and humans

In light of the highly regulated nature of the pharmaceutical industry, it is imperative that a strategic approach to implementation is taken. However, there remains huge opportunity for industry 4.0 to enhance manufacturing processes. One such technology is factory automation, which makes production lines more efficient, enhances resource effectiveness and improves productivity. Although seemingly simple to integrate, they can be complex to manage on a daily basis. "Factory automation is probably the simplest application of robotic process automation," says Taylor. "But these technologies, especially if they're going to have connected sensors embedded in them, are very sensitive to change and need to be highly monitored."

"You will always need new types of staff to make sense of all the information that is being generated, so you'll need data scientists, and analytical skills and talent."

Cobots, or collaborative robots, are expected to be increasingly used within manufacturing. Recent research has predicted this market will grow from $710 million in 2018 to $12.3 billion by 2025. This is largely due to the technology being safer, more adaptable and compact than ever before. However, such technologies are not yet able to replace humans. "There is a need for human-in-the-loop, but you

PFEIFFER VACUUM

CONTAINER CLOSURE INTEGRITY TEST

Innovative solutions for the pharmaceutical industry

Pfeiffer Vacuum provides a broad range of integrity test solutions with and without the use of a specific tracer gas. No matter if you are searching for a highly sensitive test method for your laboratory or reliable and fast testing for your production process, our solutions are applicable to different types of packaging such as vials, syringes, plastic bottles or pouches.

- High sensitivity – detection of 1 µm holes and below
- Large detection ranges – no need for separate gross and fine leak test
- Easy to use – automatic calibration based on traceable calibrated leaks and go/no-go result
- Deterministic and non-destructive testing with trend analysis, 21 CFR part 11 compliant
- USP 1207 compliant solutions, compatible with different kinds of packaging
- Process support for GMP qualification of your test process

Are you looking for a perfect vacuum solution? Please contact us:
Pfeiffer Vacuum, Inc. · USA · T 800-248-8254 · F 603-578-6550 · contact@pfeiffer-vacuum.com · www.pfeiffer-vacuum.com
ATC (Advanced Test Concepts) · Indianapolis (USA) · T +1 866 282 4621 · www.atcinc.net

probably won't need as many humans," explains Taylor. "You are already seeing that in the car industry and in other industries where you've got highly automated processes."

Such technologies might not result in an overall reduction of workers because of the increased demand in other aspects of manufacturing. "You will also need new types of staff to make sense of all the information that is being generated, so you'll need data scientists, and analytical skills and talent, which haven't been something that has traditionally been needed," explains Taylor.

A 2018 Deloitte report indicated that whilst companies are increasing their expenditure on their operational and IT budgets, they are reducing their R&D budgets. On average, they are spending 30% of their operational/IT budget on digital transformation but only 11% of their R&D budgets on this area.

One cost-effective solution to this issue might be to outsource, rather than recruiting or training in-house. "These individuals are in short supply and that's where maybe the best solution is to partner with people and companies who have those skills," says Taylor.

This strategy is already being adopted within the industry. "If you look at some of the most effective supply chains, and some of the big tech companies that have made an art form out of the supply chain, there's a lot that can be learned from when they partner together to obtain skills that are in short supply in the open market," explains Taylor.

There are also a number of emerging technologies which are likely to become increasingly implemented, such as digital twins. These are exact virtual replicas of physical products or processes, which can be updated in real time. They could be used to run simulations and machine-learning technologies could be implemented to predict breakdowns and schedule maintenance.

Virtual, augmented, and mixed reality is another valuable tool for the industry. This can be integrated into manufacturing in a number of different ways. For example, this technology can be used to design a new product, which can be refined in the virtual world before developing a prototype to test further. It could also be used to get support from an engineer remotely who could use mixed reality to be able to see what the problem is in the manufacturing process and quickly rectify it.

In addition to new technologies, industry 4.0 also opens up the possibility of transforming the infrastructure of manufacturing. In the past, information technology (IT) and operational technology (IT) OT were typically separate in manufacturing businesses. IT was responsible for supporting management, sales, accounting and purchasing whereas OT was involved with monitoring and controlling equipment, tools and other assets on the factory floor. In addition, they were not only distinct but individual systems and equipment within the OT infrastructure also existed in their own silos.

The integration of new technologies provides the opportunity to integrate machines, platforms and systems across all units of the business. This drives efficiencies, enhances business oversight, improves product quality and increases productivity. Industry 4.0 also brings challenges, of course, including dealing with compatibility issues and ensuring systems are secure. Overcoming these challenges is possible, though, presenting considerable opportunities for manufacturers.

94%

Respondents to Deloitte report that rated digital as a top priority.

Deloitte

Alike the world over

Despite the opportunity for these technologies to improve manufacturing processes, they do raise new issues. "With all of these, you get new challenges, like data security, privacy, cyber, all of those are as a result of the innovation on the one hand, raising challenges on the other side," says Taylor.

"If you look at some of the most effective supply chains, there's a lot that can be learned from when they partner together to obtain skills that are in short supply in the open markets."

A 2015 Deloitte report found that the level of cybersecurity risk could increase strongly (35%) or very strongly (48%) among respondents across a number of industries as a result of industry 4.0. Both cyberattacks and viruses could be hugely problematic, causing networked and smart production systems to a halt, creating substantial costs. However, such difficulties are not insurmountable but they do

Industry 4.0: a short history

Although the term 'industry 4.0' is widely used, it is rarely defined. Deloitte has described it as involving a move from traditional linear data and communication towards real-time access to data and intelligence. As part of this shift, there is a need for the integration of digital information from many different sources and locations can drive the physical act of doing business, in an ongoing cycle. Real-time access to data and intelligence is driven by the continuous and cyclical flow of information and actions between the physical and digital worlds, known as the physical-to-digital-to-physical (PDP) loop. This consists of three stages:

1. **Physical to digital:** information is used from the physical world to create a digital record.
2. **Digital to digital:** information is shared to create insights using advanced analytics, scenario analysis and artificial intelligence.
3. **Digital to physical:** algorithms are applied to translate digital-world decisions to effective data, to spur action and change in the physical world.

In order to achieve this, industry 4.0 combines a variety of technologies, including analytics, additive manufacturing, robotics, high-performance computing, natural language processing, artificial intelligence and cognitive technologies, advanced materials and augmented reality.

Source: Deloitte

require tailored risk management and security strategies to be put in place. It is also important to note that as technologies continue to develop, this will also bring an improvement in cybersecurity systems. The limiting factor will largely come down to implementation, rather than technological capability.

When integrating these systems, it is important that they can both prevent and treat cyberattacks effectively. Although there is increasing discussion about both the challenges and opportunities for industry 4.0, implementation is still at an early stage. "There are a number of global surveys that my colleagues have done which show that in terms of digital maturity and the adoption of technology, life sciences are lagging behind some of the other industries," says Taylor. "However, we cannot underestimate the impact that the regulatory environment has. It is an enabler for innovation but at the same time also stymies it because of concerns about meeting the requirements."

Inertia creeps

In light of the increasing technologies available as well as both the opportunities and challenges they bring, many companies remain in inertia. A Deloitte report entitled 'The industry 4.0 paradox', highlights the discrepancy between the enthusiasm for these technologies and the implementation of them in a survey of 361 executives across 11 countries.

The first of these is the strategy paradox. Nearly 94% of respondents identified digital transformation as a top priority but this didn't correspond with exploration within their organisation. Interestingly, only 68% believed industry 4.0 was an avenue for profitability, which likely is part responsible for this incongruity.

The supply chain paradox was also prevalent. Although this was an area indicated to be fruitful for both current and future investment by executives, those outside the C-suite who were more heavily involved with the daily management of the supply chain, did not have a voice in decisions about digital transformation investments.

Another paradox was present with regard to talent. Despite respondents asserting confidence that they had sufficient capabilities within their organisation for the implementation of industry 4.0, with only 15% admitting that any changes to skill sets of workers was necessary. However, they also acknowledged that obtaining, training and retaining the right people was an ongoing challenge.

Innovation was the subject of the fourth paradox identified. Executives reported that their strategies around industry 4.0 largely revolved around improving existing operations, rather than using them in a more transformative way. In light of the huge potential for innovation of manufacturing processes, such opportunities should not be overlooked.

Make the most of the opportunity

Although there is a tendency to want to make dramatic and rapid changes, it is better to start with smaller stakes, testing and refining, before scaling up where the consequences are more significant. This can help to gain confidence in the capabilities of these technologies, ultimately leading to greater innovation. Above all, it is important that companies do not expect perfection from industry 4.0. It is still evolving and it is important to learn from previous experiences to inform future initiatives.

Continuous job well done

Bosch Packaging Technology is taking on the challenges of continuous manufacturing with a new approach – the Xelum platform, based on proven fluid bed technology doses, APIs and excipients as discrete masses.

Continuous manufacturing is leading to fundamental changes in oral solid dosage (OSD) production. Higher flexibility, shorter development times with minimum API usage, and a direct transfer from development to production without scale-up are among the primary requirements of pharmaceutical manufacturers. Bosch Packaging Technology is tackling these challenges with a novel approach called Xelum. In continuous manufacturing, the processes occur one after the other without interruption, the product is charged and discharged simultaneously. The main challenge is the precise dosing of the starting materials in a constant mass flow rate of milligrams per second. Bosch uses a different approach.

The Xelum platform doses active ingredients and excipients as discrete masses and not as a continual mass flow. The system doses, mixes and granulates individual packages, so-called X-keys, which continuously run through the process chain and are discharged successively as granules, tablets or capsules. This way, even smallest amounts of APIs of less than 1% can be dosed precisely.

A novel approach to continuous manufacturing: the Xelum production platform.

The Xelum R&D unit considerably reduces development times.

Unique and proven technology

Bosch relies on a unique and proven technology. As opposed to the usual twin screws, the Xelum platform works with the more robust fluid bed processors. These processors are based on the well-known technology developed by the esteemed Bosch subsidiary Hüttlin.

In the fluid bed, granulation and drying take place in the same process chamber. This eliminates the need to transfer wet granulate, which has a positive effect on the system's reliability. Pharmaceutical manufacturers obtain granules with the desired characteristics – including unimodal particle size distribution, as well as excellent flow and tableting properties combined with high production yields. Xelum ensures lower production costs and high flexibility. The same is true for the Xelum R&D and pilot unit – an ideal start to the realm of continuous manufacturing.

"The system doses, mixes and granulates individual packages, so-called X-keys, which continuously run through the process chain."

It is the first R&D machine to combine charging, dosing of several ingredients and blending, with granulation, drying and discharging in one unit.

The shortest way from the lab to production

It is also the first unit that allows the user to develop formulations for both batch and continuous manufacturing on the same machine. Thanks to a reduction insert, the minimum amount of product that can be produced on the machine is 250g. In an automatic cycle, however, the Xelum R&D can run products at a rate of 10kg/h, which makes it useful not only for R&D but also for pilot production. As a fully closed and contained unit, it is also perfectly suited for the development of very potent APIs. Transferring processes from laboratory to production is a further challenge when it comes to traditional batch processes. This risky and time-critical stage is eliminated in the Xelum R&D system.

Since it uses exactly the same components as the Xelum production platform, process parameters are identical and can be directly transferred 1:1. Scale-up becomes obsolete, which significantly reduces development time, as well as API usage.

In this way, the Xelum platform fulfills all the requirements to realise a modern pharmaceutical OSD development and production. ●

For further information

www.boschpackaging.com

Bringing new life to your project.

Your facility design involves multiple players. Bringing them together early allows the team to provide cost certainty and higher stakeholder engagement. Find out how lean management principles can translate to real-world savings at **burnsmcd.com/LeanDelivery**.

BURNS McDONNELL

CREATE AMAZING.

Offices Worldwide

Build big and reap the advantages

Mike Glenn, business development manager at **Burns & McDonnell**, with over 35 years' experience within the field, details the importance of focusing on how a product will come to life and achieve the projected outcome.

In the life science industry, owners are looking to adapt to broad changes in the sector and be able to provide flexible solutions that are ready to be deployed quickly. Large and ageing facilities often have central plants that need to be modernised and modified, as well as environmental and water treatment capabilities that require improvements. To meet these challenges, Burns & McDonnell is helping clients integrate lean management principles, processes and tools to attack the sources of waste.

When developing a product, it is key to keenly chaperone each aspect of a convoluted process.

Keep it lean: a small, dynamic process that plays to its strengths

Incorporating lean management principles with a collaborative, aligned team and contract structure can improve the outcomes of construction projects.

By proactively identifying and eliminating the sources of waste in project delivery, owners can benefit from reduced costs, and timetables.

Turn the traditional on its head: change the approach to better the reward

Instead of focusing on the 'what' of a project, companies that consider placing greater emphasis on 'how' a project will be designed, constructed and ultimately delivered can add significant value for the owner and company as a whole.

"Instead of focusing on the 'what' of a project, placing greater emphasis on 'how' a project will be designed, constructed and ultimately delivered can add significant value for the owner."

Together with a fully integrated team approach to design and delivery from the early stages of a project, these two concepts can translate to big advantages for an owner. First, a central aspect of the approach is placing a greater focus on the owner's needs and determining the conditions of satisfaction that are unique to each owner. These conditions of satisfaction are then used as a gauge throughout the project, guiding project decisions and uniting the team around one common goal.

This means from the early stages of a project, the key members of a project team – including engineering, construction, trades, vendors and designers – work together to bring their own experience and ideas to the table. With all these voices coming together, the team is able to identify more effective, efficient and innovative ways to deliver a project while still honoring the owner's conditions Focusing on the 'how' rather than the 'what' also adds opportunities for the team to identify waste – whether it's unnecessary motion, ineffective timing of supply deliveries or overproducing materials that aren't needed – and create strategies that would reduce or eliminate the waste. This flips the more traditional "value engineering" approach that seeks to reduce cost by eliminating scope (the 'what') to a more outcomes-based focus on eliminating waste from the overall delivery process (the 'how') and ultimately delivering greater value.

Waste not, want not: a targeted approach to reduce cost in design and production

By targeting waste, the team significantly reduces project costs and often shortens the project's schedule, all while delivering a product that more directly speaks to a client's specific needs.

By offering owners a new outcomes-based approach to construction projects, waste can be eliminated and the focus can be shifted to the elements that add value. ●

For further information

www.burnsmcd.com

bea TECHNOLOGIES

BEAPURE a full line of "Animal - Free" Filters for LIFE SCIENCES

www.bea-italy.com

BEA TECHNOLOGIES — PURE — ANIMAL FREE — PRODUCTS — BEAPURE

BEA TECHNOLOGIES

*Is an italian company, based near **Milan** city, active in the design and manufacture of filtration systems focused in **pharma applications**.*
Bea Technologies** produces in a **certified cleanroom**, a wide range of filters and sterilizing membrane cartridges, according to GMP requirements, to guarantee the **quality and performances.

Via Newton, 4 - 20016 - Pero (Milano) - Italy | Phone +39 02 339 271 | Fax + 39 02 339 0713
info@bea-italy.com

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. It has paid specific attention to small and medium-sized companies and new production processes.

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 incorporates filterelements 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 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 consulting supplier to enables clients of life science to leverage filtration and separation to obtain the best cost-effective clarification of products and to achieve the safety and quality prescribed for the therapy.

"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 containing borosilicate fibres and nanofibres for high-performance filtration of viscous solutions in drug-manufacturing processes.

Together with filters based on polyethersulfone membranes, POSINYL completes the series of membrane cartridges used for the sterilisation of liquids and for the removal of lendotoxins in drug manufacturing processes.

The consistent experience of BEA Technologies and implementation of the BEAPURE concept provides a value and the services to support customer's process to obtain highly-safe products.

BEA Technologies, which 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 technology products to filter both solid particles and microorganisms, removing them from liquids, air and gas. Internally, the company is structured in such a way as to be able to guarantee, through its commercial service and laboratory service (SLB), timely and expert consulting service and commitment to stellar after-sales assistance.

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

Quality assured: dedication to maintain innovation

The headquarters in Pero, just outside Milan, is based on three facilities that occupy a surface area of 12,000m^2.

In the plant there are two cleanrooms where the company produces all its membrane filters and filter elements for use within the 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-wide good manufacturing practice (GMP) requirements. ●

For further information

www.bea-italy.com

IN A HIGHLY COMPETITIVE MARKET YOU NEED TO GIVE YOUR BUSINESS THE EDGE

When you want a clear picture of how your pharma business is performing across multiple sites and departments, NSF's EDGE Analysis can bring every detail of your quality systems into sharp focus.

NSF EDGE Analysis examines your people and processes in detail, identifies areas of improvement in your quality procedures and gives guidance on overcoming shortcomings that may risk your next regulatory inspection or limit your company's effectiveness.

Whether the answer lies in simplifying complex procedures, setting new standards or introducing new expertise or processes, NSF EDGE places a team of leading industry expertise into your business to ensure your quality procedures go beyond compliance and upgrade business performance for the long term.

In times of change knowing how to change can be difficult. Let NSF support your company to be the best it can be.

Our toolkit defines: **E**valuation, **D**iagnosis, **G**uidance & checks for **E**ffectiveness

WHY DO SUCCESSFUL PHARMA COMPANIES HAVE THE EDGE?

Because they are relentless in seeking the reality of every situation and they never stop asking these questions:

How does my PQS compare to cGMP expectations?

GMP SCORECARD & SELF ASSESSMENT TOOLS

Qualitative and quantitative benchmarking toolkit to identify key gaps in operation and quality system.

How should I manage a regulatory inspection?

GMP REGULATORY INSPECTION MANAGEMENT

Detailed coaching, tools and practice on how to prepare for, execute and follow up a GMP regulatory inspection.

How can I reduce complexity and set clear, unambiguous standards?

SIMPLIFICATION & HUMAN ERROR REDUCTION PROCESSES

Tools and coaching on how to make systems and procedures more straightforward to follow, less prone to error, faster and easier to manage.

How can I ensure our quality mindset assure company performance for the long term?

QUALITY MINDSET FOR LONG TERM SUCCESS

Tools and coaching on how to change the quality mindset of your team, underpinning any necessary change with the right approach and culture.

How do I install education rather than training?

EDUCATION ROUTE MAPS, NOT TRAINING

Integrating your training into an education programme that is inspiring, durable and fit for purpose.

How do I set standards for education and delivery?

STAFF CERTIFICATION PROGRAMMES

Setting key roles to an education programme that is assessed for effectiveness and proficiency.

Call us on **01751 43 29 99** or email us at **edge@nsf.org**

NSF INTERNATIONAL | PHARMA BIOTECH

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF

T +44 (0) 1751 432 999 | **E** edge@nsf.org | **www.nsfpharmabiotech.org**

Child's play

Meeting both regulatory and patient needs in packaging of pharmaceuticals can be highly challenging for manufacturers, especially in the case of child-resistant packaging. There are terms of legislation and certification processes to consider. Lynette Erb speaks to **Stephen Wilkins**, CEO of the Child Safe Packaging Group, to discuss meeting said requirements.

Packaging can make or break a product in any retail market. How a product is presented to the consumer can have a direct impact on sales.

In the pharmaceutical world, however, package design is about more than materials, colours and typefaces. The design of a package can also affect the consumer experience, patient adherence and disease outcomes, impacting the success – and sales – of the treatment.

However, medicines with poorly designed or manufactured packaging that fall into the hands of children can have disastrous consquences for the marketer and for the community.

Poisonings rank fourth after road traffic accidents, fires and drowning as the highest cause of unintentional death among children aged from one to 14, according to the World Health Organisation's World Report on Child Injury Prevention. Death rates are highest in children under 12 months due to their smaller bodies being more susceptible to toxins, but infants are in fact at the highest risk of accidental non-fatal poisonings.

The World Health Organisation recommends child-resistant packaging for all potentially harmful agents, including prescription and over-the-counter medicines, and high-risk household products. The choice of packaging and packaging suppliers

therefore becomes a key component in the development of any pharmaceutical product. Various standards (see boxout, page 86) govern the packaging of medicines and medical devices. The International Organisation for Standardisation (ISO) defines 'child-resistant packaging' as "packaging that is difficult for a child younger than 52 months to open but not difficult for an adult to use properly".

"If the manufacturing is slightly inaccurate and you have the basis of a peel on the lidding foil, then children will invariably pick at that until they open it."

Stephen Wilkins, chief executive of the Child Safe Packaging Group since its formation in 1995, says most standards are voluntary, and written to create a better offering to customers and to generate competitive advantage.

"They become mandatory when cited in regulation," Wilkins says. "This is the case with ISO 8317:2015, ISO 14375:2018 and ISO 28862:2018. The US regulation 16CFR1700.20 – because it is a regulation not a standard – is also mandatory."

Wilkins, as director the UKAS-accredited Davies Development and Testing Limited, tests child-resistant packaging under various international standards.

While not all products are required by law to have child-resistant packaging, the pharmaceutical and retail industries have been proactive in driving demand for best-practice packaging. For example, some products manufactured by the pharmaceutical sector – such as high-alcohol content mouthwashes – are not regulated but generally feature child-resistant packaging as an industry standard.

Wilkins emphasises the importance of drawing a distinction between 'child-proof' and 'child-resistant'. "No packaging can be described as 'child-proof'," he says. "If it were child-proof it would also be adult-proof – for example, a bottle of wine if you don't have a corkscrew could be described as adult-proof."

There's also no such thing as a child-resistant closure. "There's a closure designed to be child-resistant when tested with a suitable container – together they become a child-resistant pack. But if you put the closure on another container, it would cease to be child-resistant until it passed a test with the new container."

The standards cover all packaging, including certain drug delivery systems – for example, systems that dispense acid-based solutions to kill warts. "A system like this or, for example, an inhaler, might be unique to the pharmaceutical company," says Wilkins. "Often in these cases, the pharmaceutical company works with their packaging manufacturer to develop and test packaging that meets their requirements." Pharmaceutical companies generally either buy from an existing portfolio of products from a packaging manufacturer, or work with that packaging partner to develop a bespoke design.

Withstand the test

Packaging is tested in accredited labs to ensure it meets industry standards. To win approval as child-resistant under ISO 8317 or ISO 14375, packaging must pass two tests: a child test and an adult test.

For the child test, a pack is given to a panel of children in conditions designed to recreate real-life scenarios. "What we are trying to replicate is where a pair of children get hold of mother's medicine or father's cough drops or some household products under the kitchen sink," says Wilkins. "They have five minutes before they witness a 'silent demonstration' whereby an adult opens a pack without explanation or without emphasis on any single action. They are then given another five minutes to see if they are able to open it."

A variable sample with sequential testing is used. or packaging to pass, 80% of children must fail to open it having seen the demonstration, and 85% must fail to open the pack prior to the demonstration.

The child test is followed by an adult test, whereby the packaging is tested for functionality to ensure it can be accessed by its target user. The adult test requires a simple 90% success with a panel of 100 adults aged 50–70 (70% female). Adult-friendly packaging must be 'easy' and 'obvious' to access. ▶

Child-resistant packaging is vital in deterring children from accessing potentially hazardous materials.

"The adult test is really just a benchmark – 50–70 years of age obviously doesn't reflect the population," Wilkins says. A 100% adult success and 30 child successes in a row with no failures would be regarded as a 'clean pass'.

Packaging manufacturers will either arrange this testing for new packaging on behalf of a pharmaceutical company, or provide packaging that's already tested and certified. "The IP of testing belongs to the organisation that commissions the test," says Wilkins. "A pharmaceutical manufacturer therefore may well decide they want the IP for themselves rather than buying a standard product from the packaging manufacturer."

Failure to launch

Wilkins estimates his company sees less than a 15% failure on the packs they test. Responsibility for a rejected package would rest on the company marketing the product, but substandard or faulty packaging would also force the packaging manufacturer and others in the supply chain to reassess their processes.

"If a pack is properly designed and properly manufactured it's not going to fail," says Wilkins. "In terms of blister packs, if the manufacturing is slightly inaccurate and you have the basis of a peel on the lidding foil, then children will invariably pick at that until they have picked off all the lidding foil and open it."

Relevant ISO standards

There are various International Organisation for Standardisation (ISO) standards relevant to medical and household products:

- **ISO 8317:2015:** International standard, reclosable packs (any contents)
- **ISO 14375:2018:** the international standard, non-reclosable packaging (medicines)
- **ISO 28862:2018:** the international standard, non-reclosable packaging (non-pharmaceutical products)
- **ISO 13127:2012:** packaging tested under ISO 8317 but later altered

National standards

- Human Medicines Regulation 2012 No. 1916 in the UK covers over-the-counter medications including aspirin, paracetamol, iron, and children's cough medicines.
- Other European countries have their own regulations for medicines.
- Prescription medications packaging standards are generally industry-led, and covered via pharmacy practice direction from bodies such as the Royal Pharmaceutical Society in the UK (or the EU country equivalent).
- EU reg 1272/2008 covers non-medicines.
- The Tobacco Products Directive in the EU covers tobacco products and nicotine replacement products.

Relevant organisations

- **UKAS:** United Kingdom Accreditation Service
- **BSI:** British Standards Institute
- **ISO:** International Organisation for Standardisation
- **CEN:** Committee European Normalisation

Failures usually involve packaging manufacturers who are new to the market and make simple errors. Failures can also occur if you try to design something that's highly sophistociated. "If you're going to make something that's going to jump off the shelf at the customer – which is what packaging needs to do in order to have tremendous shelf appeal – you might, for example, try and design something with a flip top that opens the opposite way to regular flip tops," Wilkins says. "However, you need to ensure it doesn't become so counterintuitive that it fails the adult test." To prevent issues like this, you could pilot test it first with a very limited sample, which would give you an indication of whether it looks likely to pass. Wilkins also recommends packaging manufacturers attend a testing procedure as part of their design and development phase. "In designing a pack you can then see how children attack packs and what the pack has to do," he says.

This can be hugely eye-opening for designers, who quickly realise that there are no rules when it comes to children. "They will chew up and spit out certain materials, so you need to use more adhesive in constructing your packaging than would be necessary for adult use," Wilkins says.

There are a number of creative strategies that can be used to achieve child-resistant packaging. "You make something child resistant by making children do two simultaneous things like squeeze and turn, or push and turn," Wilkins explains. "So you could have a box made of carton board where you would squeeze the edges and pull the slider out – that would defeat children in terms of access, but they could actually chew up the carton board. So you would need to look at using a laminate board or more adhesive or another method to prevent children from accessing it."

Not to be boxed in

Wilkins says the adult component of the child-resistance test can be an effective means of determining whether a product will meet customer expectations. "If someone buys your product and they cannot open it, they are probably not going to buy it again," he says.

The additional materials needed and the more sophisticated element of design needed for child-resistance can increase costs, says Wilkins. "But in return you're getting a child-resistant pack thatis either required because you have a regulated pack or it's demanded by your customer."

He says this presents an opportunity to value-add. "You might have two layers of material where a standard pack would only have one – can you make it into a compliance pack or into an anti-counterfeit pack as well to add further value or broaden the appeal?" he concludes. ●

Top treatment for customer cargo

AirBridge Cargo (ABC) is one of the world's global cargo airlines, and its expanding route network connects customers in the largest trans-regional markets of Asia, Europe and the US, covering more than 30 major cargo gateways and accommodating trade flows worldwide. All the flights are operated via ABC's cargo hub in Moscow Sheremetyevo Airport, guaranteeing seamless connection throughout the airline's expanded international network within a 48-hour delivery period, including handling. ABC's fleet of Boeing 747 freighters is one of the youngest and modern in the airline industry.

ABC is the best partner, with an in-depth knowledge of the healthcare and pharmaceutical industry. The company's speciality product, abc pharma, offers the following benefits:

- exact temperature monitoring from acceptance to delivery
- special packaging solutions and thermal blankets for palletised shipments;
- abc pharma Active and abc pharma Passive solutions – the first is for time and temperature-sensitive pharmaceutical products that need to be shipped in active containers (including dry ice technologies), and the second is for prepackaged pharmaceutical products
- dedicated, skilled staff trained in handling healthcare products
- full compliance with IATA TCR and CEIV certification
- envirotainer QEP-accredited stations within ABC network
- customer service support, online track-and-trace option for all shipments
- Boeing 747-8 and 747-400 with three compartments enabling different temperature settings of 4–29°C
- fast temperature pull down times after take-off
- temperature-controlled facilities on majority of stations throughout the ABC network
- high-tech pharma hub at Moscow Sheremetyevo International Airport with effective connections to deliver cargo worldwide
- sophisticated, cohesive and forward-thinking approach based on peer learning and networking through industry-related initiatives
- 24/7/365 Control Tower (CT) operation to monitor and manage transportation of special cargo consignments
- adoption of the latest digital technologies, such as Sky Fresh; for automated notifications, temperature data loggers to monitor consignment conditions.

ABC promises a delivery time of within 48 hours, including handling.

Further information
AirBridgeCargo
www.airbridgecargo.com

High grade hits the market

CBDepot's work has been constantly driven by innovations. 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 world's biggest pharmaceutical event, the CPhI in Frankfurt, Germany, in October 2017, through its contract manufacturing partner, Vakos XT.


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

In November 2017, 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 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 with CBD, and reports the best outcomes when CBD of natural origin is being administered to his patients. In 2019, again through Farmakem, this active substance has been 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

Low-endotoxins for pharmaceutical applications

Endotoxins or pyrogens are lipopolysaccharides – outer membrane components of gram-negative bacteria. During decomposition or metabolism, these bacteria release lipopolysaccharides, which are toxic. Parenteral-induced quantities as low as 0.1ng/kg of body weight can cause various immune reactions, including fever, inflammation and sickness in humans and animals. To avoid this, the manufacture of products for parenteral administration requires particular caution; it is subject to specific regulatory requirements and is regulated by chapter 2.6.14 of the European Pharmacopoeia (PhEur).

Dr Paul Lohmann's state-of-the-art production unit allows a manufacturer to comply with quality and regulatory requirements, and satisfy increasing volume demands for mineral salts in parenteral applications. The company's production sites are GMP and DIN EN ISO 9001:2015-certified, and LAL tests according to PhEur are performed on each batch. Customers can seamlessly integrate Dr Paul Lohmann products, which are low in endotoxins, into their process chain for the manufacture of parenteral dosage forms.

Low-endotoxin mineral compounds can be used for the production of three pharmaceutical forms and routes of administration:


Low-endotoxin compounds can be used for many pharmaceutical forms.

- **Parenteral:** intravenous, intra-arterial, intramuscular and subcutaneous.
- **Dialysis:** peritoneal dialysis, haemofiltration and osmotherapy.
- **Ophthalmic**.

Pharmaceutical manufacturers of preparations for infusion or injection are obliged to observe special regulations specified by the relevant pharmacopoeia and good manufacturing practices. Dr Paul Lohmann emphasises that its products are low in endotoxin content, but not entirely endotoxin-free and not sterile. Therefore, these products must be treated with special procedures prior to their use in finished pharmaceutical products. The pharmaceutical manufacturer must ensure that these products undergo special procedures and tests prior to being processed for infusion/injection preparations in order to guarantee their suitability for purpose.

Further information
Dr Paul Lohmann
www.lohmann4minerals.com

The new frontier for selected drug shipments

Gold Ice and Silver Ice by Dryce are a new bio-based and biodegradable phase-change material (PCM) family, available for passive packaging solutions conditioned at 2/8°C and at 15/25°C.

These products, different from the old generation of water-based PCMs, show a significant thermo-physical property, truly appreciated into cold chain of thermal sensitive drugs and diagnostics. Silver Ice is a bio-oil with a melting point at 5°C, and Gold Ice is a similar product with melting point at 21°C. Using Silver Ice is possible to stabilise the

Gold Ice is a biodegradable vegetable oil with a solidification point of 21°C.

temperature inside a passive packaging, as well as a pallet shipper or any parcel solution, at 5°C, avoiding any risk of under-cooling, since the working temperature of this PCM is just 5°C. The same happens for the Gold Ice solutions, where the optimal temperature is maintained at 21°C, since this is the melting point of Gold Ice PCM. The passive thermal solutions configure with innovative PCMs and work excellently in all seasons, reaching up to 120 hours of temperature control.

The secondary advantage related to the use of Silver Ice and Gold Ice comes with the simplification of PCMs activation and assembly procedure. Since Gold Ice is activated at 5°C and Silver Ice at 21°C, it's enough to put them in a simple fridge for a few hours, in order to get them fully activated. Then since it's needed to use just a single thermal mass, only Silver Ice for 2°/8°C and only Gold Ice for 15°/21°C temperature of shipments, the assembly of any passive packaging in any configuration comes really easy and is error-proof.

Silver Ice and Gold Ice are biodegradable materials, made of bio-based products. This helps end users to adopt a new eco-friendly solution, in single-use thermal packagings, reducing the disposal costs while doing something good for the environment.

Further information
Dryce
www.dryce-pharma.it

Supporting research for the clinical use of cannabis

The International Cannabis and Cannabinoids Institute (ICCI) supports and coordinates global research efforts for the clinical use of cannabis, as well as the nutritional and industrial applications of hemp. It offers a strong multidisciplinary team, a favourable legal environment and a network of international contacts to its clients.

ICCI is headquartered in Prague, Czech Republic,and joins researchers in various aspects of cannabis science with patient organisations, and legal and regulatory experts supported by the investment company Dioscorides Global Holdings. ICCI functions as a centre of excellence that unites 29 Czech companies and institutions, with Hebrew University in Jerusalem and many others around the globe. Its clients currently include countries on every continent outside of Antarctica. Its physicians and healthcare experts can support any aspect of clinical development, whether it be for pharmaceutical approval via the European Medicines Agency (EMA), Health Canada, or the US Food and Drug Administration (FDA), for the supplement market, or artisanal preparations. It can guide companies through the intricacies of national and international law that are necessary to this burgeoning new industry.

An additional mission of ICCI is the promotion of cannabis education, from continuing medical education (CME) for physicians to on-the-job practical education for cannabis

ICCI seeks to answer any and all queries about medicinal cannabis.

analytical laboratory workers, and even dispensary personnel. ICCI supports standardisation of cannabis preparations, and promotes good agricultural, manufacture, laboratory work and clinical practice, through provision of educational and inspection services.

ICCI also promotes in-house research, designed to investigate issues related to cannabis, therapeutics and nutrition. "ICCI provides the ideal platform to explore unanswered questions concerning cannabis and its applications for human health," states Ethan Russo, MD and director of research and development.

Further information
ICCI
www.icci.science

Electronic devices to improve patient adherence

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

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

There are several factors that can attribute to low adherence rate, such as a lack of understanding by the patient about the condition of following a strict treatment schedule, uncomfortable side effects of the medication as well as difficulty in administering the treatment. e-Novelia has been conceived to make patients' lives easier, by offering an increased comfort of their treatments. Nemera designs, develops and manufactures devices that truly improve patients' lives for nasal, buccal, auricular, inhalation, dermal and transdermal, parenteral and ophthalmic delivery.

In particular, Nemera provides millions of multidose eye droppers for preservative-free formulations. With an ageing population and increasing numbers of patients suffering from chronic eye conditions that require regular topical treatment, it is 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 understanding by the patient about the condition and the necessity of following a strict treatment schedule, uncomfortable side effects of the medication as well as difficulty in administering the treatment, to name a few. This is why Nemera has developed e-Novelia, a new electronic add-on technology, providing more features than standard eye droppers already existing on the market. e-Novelia has been conceived to make patients' lives easier, by offering 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 to all stakeholders involved. This includes healthcare practitioners and pharmaceutical companies.

Nemera's innovative devices appear at several events in following months, including CPhI Worldwide in Madrid between 9–11 October.

Further information
Nemera
www.nemera.net

A new series of thermal analytical instruments

Nevio, the new series from NETZSCH, is specifically designed for the challenges of quality control, and research and development, in the pharmaceutical, cosmetics and food industry. The portfolio on offer includes the two complementary thermal analysis methods, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The combination of the two methods, along with the ability to couple gas analyser systems to thermal analysis, facilitates interpretation of detected effects.

SmartMode, for intuitive use of the measurement software.

The Nevio instrument series also supports the determination of the eutectic purity and product degradation, and is capable of giving first information about compatibility between various components in a physical mixture. TGA in particular can be applied in determining the shelf life (derived from thermal stability) of a product under a given set of storage conditions.

Such challenging tasks require sophisticated analytical tools. With a view to quality control, it is crucial that laboratories apply well-established, recognised methods on robust and reliable instrumentation that is suitable for operation within the given regulated areas. The NETZSCH Nevio instrument line comes with Proteus Protect, an add-on to the successful Proteus software, which ensures data integrity at a high level and meets the requirements of 21 CFR Part 11 or EU Annex 11.

Further information
NETZSCH
www.netzsch.com/at

High-compression turbopumps arrive on the market

Pfeiffer Vacuum is presenting extremely high-compression models with its brand new HiPace 700 H turbopumps. With a compression ratio of $\geq 2 \cdot 10^7$ for hydrogen, they are suitable for generating high and ultra-high vacuum. Due to the high compression ratio, a low residual gas spectrum, which is desirable for certain mass spectrometry applications, is created in the chamber.

Pfeiffer Vacuum introduces the new HiPace 700 H.

Due to advanced rotor designs, HiPace 700 H turbopumps have an inimitable backing pressure capability of 22hPa. This allows the pumps to reach ultra-high vacuum, even when operating with high backing pressures that occur in combination with diaphragm pumps.

"With the new HiPace H-family, we have the ideal turbopump for research and analytics applications as well as for other industrial applications. In terms of energy efficiency as well, this product is far ahead. Due to the integrated 'intermittent mode' function, the HiPace H switches a connected backing pump on only if the backing pressure is no longer sufficient. This reduces the energy consumption of the entire vacuum system by up to 90%," says product manager Florian Henss.Due to the hybrid bearing, combining a ceramic ball bearing on the fore-vacuum side with a permanent-magnet radial bearing, these turbopumps are equipped with a particularly robust bearing concept. As a result, they have a long service life with a service interval of over four years.

Further information
Pfeiffer Vacuum
www.pfeiffer-vacuum.com

BOSCH
Invented for life

XELUM

THE FASTEST WAY TO CONTINUOUS MANUFACTURING

- Closed and contained material handling (bin-to-bin)
- X-key principle for precise dosing and handling of the smallest amounts of API
- Up to 5 loss-in-weight feeders
- Software support for automated DoE
- Results can be transferred 1 on 1 to the production unit
- Pilot-scale production up to 10 kg/h (e.g. orphan drugs)
- Recipe-controlled operation and cleaning
- Direct connection with tablet press or capsule filler possible

See it
in operation at
Interphex, New York
April 2 – 4, 2019
Booth #3305

Hüttlin GmbH
A Bosch Packaging Technology Company
Hohe-Flum-Straße 42
79650 Schopfheim
Germany
Phone +49 7622 6884-0

Robert Bosch Packaging Technology, Inc. Pharmaceutical
8700 Wyoming Avenue North
MN 55445-1836 Minneapolis
USA
Phone +1 763 424-4700

Follow us on

boschpackaging.com

THE WORLD'S HEALTH IS IN THE SAFE HANDS OF TURKISH CARGO

As the cargo airline that flies to more countries than any other, we carry all your health and wellness needs, from pharmaceuticals to medical supplies without ever interrupting the temperature-controlled cold chain.

TURKISH CARGO

turkishcargo.com