

Securing the cold chain with new solutions

Ben Hargreaves examines the emerging practical and technological solutions that are aiming to improve patients' access to medicines in a safer and more controlled manner

Medicines are becoming increasingly complicated as scientific advances push frontiers that could previously never have been predicted. The recent approval by the FDA of the first CAR T treatment is the perfect example, created as it is by re-engineering a patient's immune system to combat cancer. Novartis's therapy has been approved following the release of some astonishing data displaying just how effective the treatment can be.

The FDA gave the okay to Kymriah, the brand name of the drug, based on clinical studies wherein 83% of patients given the treatment achieved complete remission within three months of infusion. However, Kymriah is groundbreaking in more than one way – it opens up a whole new field of personalised treatments to a previously unseen degree.

Another aspect of the scale of the treatment is the price: the drug carries a \$475,000 price tag per dose. This alone has sparked numerous debates, with the cost actually lower than some anticipated, including the UK's NICE. It is still prohibitively expensive but there are good reasons for the price, and it lies in the complicated manufacturing process.

First, patients must undergo blood leukapheresis whereby white cells are separated from blood samples. The white cells must then be cryogenically preserved en route to the manufacturing site, where the T cells are then selected and produced on a larger scale before temperature-controlled transportation back to the treatment facility, where it can finally be administered to patients.

The nature of the supply chain for this one treatment is highly complex, but this means there are opportunities within the process for companies offering cold chain solutions to work with the pharmaceutical companies developing such treatments. This has been plotted as being part of wider trend; in Corex's recent white paper, *Global Trends in Clinical Trial Logistics: 2020 Perspective*, it was revealed that 38% of pharma products are temperature-sensitive and 35% of late-stage pipeline drugs are biologics.

The temperature-controlled market heats up

The rise of biologics, which have replaced small-molecule drugs as the industry's top sellers, has led to the greater need for cold chain logistics. They are protein-based drugs that are derived from living cells and cultured in a laboratory, meaning that they are incredibly sensitive to temperature. Rheumatoid

arthritis treatment Humira, one of the most lucrative drugs in the pharmaceutical industry, reaping sales of \$16.1 billion in 2016, is a biological drug.

With over a third of drugs in late-stage development being biologically based, this means there is already a high demand for temperature-controlled transport. In addition, the rise of biosimilars, particularly in Europe but also now gaining ground in the US, should only see the dependence on cold chain logistics increase. The biotech industry slowed down briefly as a result of President Trump's election amid blusterous talk of cracking down on the pharma industry, but has since bounced back with investment recovering, perhaps best represented by Gilead's recent \$11.9 billion bet on biotech, Kite Pharma. This sign of confidence in the area is set to boost investment and there are signs that the biotech boom the US has experienced could soon be better translated to the slow-to-develop European market. Funds are now taking their money from the US to back European biotechs; for instance, the recent fund launched by Medicxi looks to funnel \$300 million into biotech start-ups to help bring their products through drug discovery all the way through to the market.

This builds on a trend already occurring that has seen the number of heat-sensitive products increase by 45% from 2011 to 2017, with such medicines now accounting for one in every two products, according to a report by Evaluate Pharma. The pharma cold chain market, as a result, is reported to be set to grow to be worth \$16.6 billion by 2021.

Boom without the bust

This rising demand, which could soon reach fever pitch, means that cold chain suppliers need to be able to meet the challenge. The traditional issues the market has faced often come down to the fundamental service they offer: maintaining a constant temperature. Ensuring that there are no 'temperature excursions', where temperature deviates from given instructions, is the principal desire of both sides of the supply chain. It is a high-stakes need as one lost shipment due to temperature-controlled failure can mean the loss of a single cargo worth millions. A study by the Georgia Institute of Technology found that 90% of failures in the cold chain are down to basic human error. The reaction to this has been to place more control in the hands of digital technology, with remote temperature monitoring and control becoming a key part of the market.

According to MHI's 2017 annual survey, 80% of respondents believe that a fully digital supply chain will be the predominant model within the next five years. 16% of respondents believe that this is already the case and that further developments will simply be adding to the existing framework. Sensors that are able to monitor temperature, location, light exposure, humidity, barometric pressure and shock will soon be an accepted part of the supply chain, and facets of each have already been introduced. There is also the ability to monitor security and integrity of products through the previously impossible creation of smart networks.

The technology of the 'Internet of Things' (IoT) remote diagnostic devices holds obvious potential for the cold chain. Live visibility of cargo as it moves through the chain would allow logistics providers to offer more reflexive and secure services to pharmaceutical companies. It also means that reports generated through these IoT devices can be submitted to regulatory authorities. This particular part of the supply chain – the specialised tertiary packaging and instrumentation, which includes insulations, phase-change materials and temperature sensors – is currently worth \$4 billion, and this figure is expected to grow commensurately with the cold chain industry and the technology itself.

Delivering practical solutions

For certain companies, more of their products need to be shipped by cold chain than not, and therefore developing technology within it can have a significant impact on the business. GSK, for example, manufactures vaccines that are transported all around the world and are entirely dependent on a consistent temperature within units for the products to survive the journey to the disparate regions where they are required.

Pharmafocus approached GSK to highlight exactly where the difficulties reside on the pharmaceutical side of the supply chain and how it is working, from its own base, to surmount the difficulties faced by the cold chain. A spokesperson elaborated some of the logistical challenges it faces when distributing around the globe:

"In 2016, GSK delivered over two million vaccine doses every day for use in 166 of the world's countries. More than 70% of these doses go to developing countries and most of our vaccines need to be stored between +2°C and +8°C. If the cold chain cannot be appropriately maintained or monitored, the vaccine may need to be disposed of," a company spokesperson explained.

"Some of our destinations are remote and hard to access. One challenge in delivering vaccines is the difference in temperature and humidity between shipping and receiving sites. For example, there's a big difference in temperature between Belgium and Brazil, or Belgium and Canada during winter, so it is essential that we have the right cold chain packaging solution in place to protect our product at all times."

With these challenges mentioned, how do you actively manage to mitigate the risks? GSK takes the aforementioned route of ensuring constant monitoring of temperature during shipping of their products:

“We need to maintain and monitor the cold chain throughout the journey of a vaccine while it is in our control. To help achieve this, we use sophisticated insulated packaging for all storage and distribution to maintain the set temperature range. As part of this process we undertake a Distribution Risk Assessment, evaluating all risks associated with the journey. We also use the latest technologies to monitor temperature of the shipment so we know at all times the temperature integrity of the shipment wherever it may be.”

For its part, GSK is also designing its own products with the challenges of the supply chain in mind. The company recently received the EMA’s Committee for Medicinal Products positive opinion for its new formulation of its pneumococcal vaccine. The product, Synflorix, has been specifically designed for the cold chain and the wider supply chain, with a design that reduces the physical space needed to transport the vaccine by 50% compared with the existing two-dose vial presentation. This makes the product the lowest volume for any pneumococcal conjugate vaccine, at 2.4cm³ per individual dose. The new formulation also allows usage for a longer period after opening, extending its use to 28 days, radically longer compared to the six hours possible with the two-dose vial.

Describing the plan for product and the intention to work with Gavi, the vaccine alliance, the GSK spokesperson commented:

“Following EMA approval, GSK will submit the new four-dose vial presentation to the WHO for prequalification. Depending on WHO prequalification and local regulatory approvals, GSK expects to start supply of the new four-dose vial presentation to Gavi-supported countries from early 2018. Upon local approval of the four-dose vial, we expect it to gradually replace the two-dose vial presentation in Gavi countries. The Synflorix four-dose vial current price is \$3.05 per dose, which is the same as the price per dose for the two-dose vial presentation. In line with our current commitment, if future efficiencies are identified that reach a meaningful level, we will look to pass these on to Gavi.”

Encoding safety through the supply chain

One challenge that all aspects of the supply chain will have to adjust to is the requirement to comply on serialisation by 2019. The move is part of a wider effort to ensure the security and traceability of medicines through the supply chain. Serialisation will involve the addition of a unique code to products passing through the supply chain. This will be enforced across the US and Europe in a bid to verify the legitimacy of a drug product down to the package level. It is hoped that the move will also do much to remove fake medicines from the supply chain, as well as easing the recall of products that have been deemed faulty. The shift carries with it an opportunity



for those who operate within the cold chain, as the rise of IoT technology means that traceability is already high and the additional requirements, though initially difficult and coming with a cost to implement, will simply add to a growing trend within the industry. The final outcome will be the fully traceable journey of the product.

Bringing the blockchain to the supply chain

One innovation that has been much-hyped across a whole range of industries is blockchain technology. The innovation came to most people’s attention through Bitcoin, the digital currency which allows money to be transferred securely without the need for a bank to function as an intermediary. In a very simplified explanation, the blockchain allows for transactions to be verified by all users of the network and are held on a public ledger for everyone within the network to see. The main benefits of this approach to the supply chain are the potential to increase security and to improve automation. It is an innovation that needs to be considered across all aspects of the supply chain, including the cold chain, as it could potentially be entirely transformative for the industry.

To provide background on the potential that the blockchain technology could hold for the pharma supply chain, *Pharmafocus* spoke to Dr Philipp Sandner, Head of the Frankfurt School Blockchain Center, at the Frankfurt School of Finance & Management. Dr Sandner was part of the team that developed LifeCrypter, a first prize-scooping blockchain solution for the life sciences industry at a recent

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hackathon event hosted in Germany.

In order to simplify the understanding of a complex area, Dr Sandner provided a brief overview of the technology and potential solutions it may provide moving into the future:

“Blockchain is a distributed storage solution that provides a way for information to be recorded and shared through a peer-to-peer community. In this community, each member maintains their own copy of the information and all members validate any update collectively through a consensus process to validate all data that is stored. This could be transactions, events or other data banks. It offers incredible solutions to problems in numerous industries by making data safer and more efficient. The main focusses nowadays are in finance, such as crypto currencies, where simple, safe and transparent transactional data and digitalisation of assets are at its core. We also see blockchain technology being used in real estate markets to efficiently oversee large data banks. In the future it can be expected to revolutionise nearly every industry that requires large data sets.”

One of those industries could well be the life sciences and, in particular, Dr Sandner points out that security

within the industry could be completely revolutionised by the emerging technology:

“We currently see hacking incidents increasing within the life sciences industry, with hundreds of thousands of patients’ private data potentially falling into the hands of hackers. Some reports even go as high as stating that a third of all healthcare recipients will be affected from these data leaks in the future. These breaches mainly result from transferring and sharing sensitive data without suitable protection. Blockchain technology offers a safe and efficient way to keep large amounts of data and transparently manage the data access. The technology is safe; but, of course, human error might still lead to problems despite the safe data storage.”

“Also, we see insufficient tracking of pharmaceutical material, which resulted in 30% of drugs sold in developing countries being counterfeits, harming people and company brands. This can also be prevented by using more efficient data storages, where all parties can track and validate the authenticity of products.”

Looking to the future, blockchain technology has been labelled as a potential disrupter of a number of industries. With the pharmaceutical industry notoriously slow at adopting and evolving alongside the emergence of new technology, *Pharmafocus* enquired as to what the future held for its function in the life sciences and how quickly it could be expected to make an impact.

“Regarding life science companies, I expect a similar bottom-top trend that we currently see in other industries. It will start with smaller companies using blockchain for data sharing and safety, and then will move up to larger



corporations once its use is confirmed...I expect it to be partly adopted in the near future, let's say six years."

He continued: "I definitely believe that the technology has a long-lasting disruptive potential for the pharmaceutical industry. It can change the way we handle sensitive data, but also change the costs and availability of research by efficiently sharing and validating data. It can significantly increase security, research and efficiency on all levels; we expect to see further applications to be seen in the healthcare industry. We are currently working together with a company that seeks to give patients control of their own data, including the potential to sell their own data on a case-by-case basis to researchers, which could eventually include pharmaceutical companies."

Daring to innovate

Pharmaceutical companies are already making tentative steps into the area, with one recent agreement enacted between Trek Therapeutics, a company focused on developing treatments for infections, and Ambrosus, a firm that is using blockchain technology within the supply chain. The collaboration is exactly in the vein that Dr Sandner references in his bottom-up example of how the process will eventually take off within the industry. Trek Therapeutics' CEO, Ann D Kwong, spoke to *Pharmafocus* about the deal and how it came about:

"Trek is collaborating with Ambrosus Partners to develop a proof of concept project to utilise blockchain technology to design a programme to drive quality, purity, integrity and for patient-centric delivery of Trek's emergent pharmaceutical products and supply chain. Ambrosus combines high-tech sensors, blockchain protocol and smart contracts to build the world's first publicly verifiable, community-driven ecosystem to ensure the quality, safety and origins of products, such as food, medicine and commodities. In a similar way, pharmaceutical companies must also monitor and control the origin of the ingredients in its drug products as well as environmental conditions such as temperature, moisture and time, under which such drug products are synthesised and stored. Ambrosus will work with Trek and conduct a pilot project using its blockchain technology to monitor feedback from sensors that Trek will embed during various steps in the manufacturing and packaging of Trek's pharmaceutical ingredients."

The fact that the deal is at the proof of concept stage is not unusual for blockchain technology's introduction into the supply chain. The nascent technology is full of potential but businesses are unsurprisingly cautious about how it may be used and how it can improve on current standards. The first purchase and shipment of any product through blockchain

technology only took place a little less than a year ago, in October 2016, when Australia-based Brighann Cotton used the technology to sell cotton internationally between two of its subsidiaries; the transaction saw 88 bales of cotton shipped from Texas in the US to Qingdao in China.

In order to illustrate why there is such an appeal to the technology that is garnering such attention, Kwong outlined: "Blockchain technology has the potential to digitally validate any aspect of the pharmaceutical manufacturing and supply chain process that can be linked to a sensor without requiring on the ground inspection. In addition, Trek is attracted to the public verification aspect that Ambrosus's blockchain technology protocol could bring to pharmaceutical drugs. Currently, patients have to trust that the drugs they buy are manufactured properly, but blockchain technology has the potential to provide the relevant information directly to the consumer for each drug."

She added: "Our aim is to develop a method to provide greater assurance to regulatory authorities, providers and patients that the medicines they regulate, prescribe and buy are excellent quality."

The security aspect, with the transparency to potential customers or patients using the product, holds a particular crossover with the forthcoming changes in the introduction of serialisation. As this will require a unique code to be scanned at every significant point through the supply chain, it should increase the traceability of the product and improve the transparency of the whole process. The two could potentially find overlap in operations to secure the security mentioned by Kwong. However, it is unlikely that major pharmaceutical companies will be keen to experiment just yet, as blockchain technology remains at such an untested level and the complexity of coping with serialisation remains an expensive headache.

Trek Therapeutics, however, is in an unusual position to be able to push an innovative mode. Kwong explained: "If blockchain technology's potential is borne out, Trek could raise the industry bar in terms of delivering quality and soundness of ingredients, and components from precursor chemicals to final package product with less paperwork and physical inspections. As a public benefit corporation, Trek is advancing a new business model in the pharmaceutical industry. Our mission is to provide affordable and accessible treatments for infectious diseases. We think our mission also embraces challenging convention to boost the integrity of manufacturing and supply chain as technology blazes a pathway.

"This is our goal. The blockchain itself is like an endless digital receipt of transactions that can be used to prove that an event occurred, or that a record exists. The technology

significantly reduces the risk of fraud or error because it is completely transparent. Our plan is to do a small proof of concept pilot project and then take it to an industry-wide stakeholder consortium – an example of such a consortium is the Hepatitis C Drug Development Advisory Group, which Trek members helped create to harmonise HCV clinical development. An innovation of this magnitude would need input from multiple pharmaceutical companies, regulators, key opinion leaders and patient groups to really gain traction. Counterfeit medications and unauthorised suppliers have compromised global public trust in the integrity of their medications. In addition, current regulatory inspections and other assurances of supply chain are cumbersome and expensive. If the logistics and advantages of this technology can be established and complement current programmes, we think there could be broad uptake. Regulatory authorities around the world would have to authorise and harmonise blockchain. But if it could deliver higher integrity products more efficiently with digital footprints, it could be roundly embraced."

Future-proofing the industry

Kwong concludes her outlook for the technology with the many ways it 'could' change the industry, and for the moment it still remains just that: a possibility. However, the key change across all industries is the rapid pace that successful technologies manage to wholly revolutionise the face of doing business. With discussions of drone delivery in the supply chain shifting from ludicrous to the plausible of late, it is necessary to bring up these new frontiers so that if, or when, they eventually gain ground then all stakeholders have been sufficiently versed in how things may change as a result.

The benefits that blockchain technology offers to consumers of the products of the life sciences industry should be one of the drivers at looking at adoption, because the value in certain areas is so pronounced. Nobody within the industry wants counterfeit drugs to make it to people who are in need of medical aid and, if adoption is able to prevent this global scourge even in a modest fashion, it would justify the effort needed to explore new methods of approaching old problems.

The technology's ability to disrupt the supply chain, including the cold chain, is still a way off, but if Dr Sandner's prediction is correct, six years is not too long a wait. Looking into the potential of such technology now could allow companies, and the wider industry, to gain significant ground before the tipping point is reached and present solutions suddenly look very much like a part of the past.