INDUSTRIALISING DRUG DELIVERY

ON drugDELIVERY

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INDUSTRIALISING DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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INDUSTRIALISATION OF DRUG DELIVERY BEYOND MANUFACTURING

In this article, Napoleon Monroe, Managing Director at New Directions Technology Consulting, considers the impact of the changing technological landscape on how industrialisation in the healthcare industry is evolving, with reference to the idea of "patients as consumers" and how the relationship between consumers, information and industry has evolved in other sectors, such as tech and retail – and how big players in those sectors are looking to move into and disrupt healthcare.

While the US drug delivery industry is already highly industrialised, it is currently poised for radical change. The healthcare ecosystem includes multiple other industries which impact drug delivery, and the covid-19 pandemic has catalysed acceptance of change in healthcare. Technology can provide tools to improve access to care and health outcomes, as well as enabling the sharing of information between industrial silos and the patient population. Drug delivery companies employing smart, patient-friendly digital technology can disrupt, or even creatively destruct, existing industrial healthcare silo models.

Figure 1: As the great detective says...

> "Digitisation and related technological advances that support the acquisition and analysis of data are the technologies currently driving the industrialisation of drug delivery and healthcare."

As noted, healthcare, including pharmaceuticals and drug delivery, is already industrialised. Articles in ONdrugDelivery's "Industrialising Drug Delivery" issues tend to be on improved products and innovation in manufacturing processes, platforms and systems, all of which are important developments. However, here we'll step outside the typical coverage to discuss the industrialisation of customer/patient centricity in drug delivery and elsewhere (Figure 1).

FOUNDATIONAL ELEMENTS – INDUSTRIAL STRATEGY AND TACTICS

There has been a great deal of discussion recently about defining the foundational elements that determine the success of a society or national economy. It is also interesting to ask about the foundational elements of the industrialisation of a given industry. These two subjects share some common themes.

Industrialisation is clearly foundational for a successful world economy. Digitisation and related technological advances that support the acquisition and analysis of data are the technologies currently driving the industrialisation of drug delivery and healthcare. Some other foundational

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necessities for the industrialisation of drug delivery and healthcare are:

- A respect for scientific principles
- Concern for the general welfare of – and providing value to – the population (patient-centricity)
- Coherent messaging of basic objectives
- Reversal of unduly restrictive laws that disadvantage broad sectors of the general population; allowing women access to birth control is a drug delivery example; and the repeal of certain tariffs that have effects similar to the Corn Laws is a more general example
- An uncorrupted legal system that is fairly and uniformly enforced
- Access to capital
- Acceptance of positive changes.

With all of those in place, some of the other foundational elements for successful industrialisation of drug delivery are an understanding of:

- Internal objectives
- Internal funding
- Drugs and their target diseases
- Onboarding, training, continuing instruction and change management
- Scalability of proposed programmes
- Markets and competitors
- Potential partners and related contractual terms
- Patient demographics
- Laws and regulations
- Reimbursement possibilities
- Traditional and novel technologies
- Trends.

Finally, once those are pretty well understood, come the harder parts – understanding patients' and other stakeholders':

- Knowledge
- Limitations
- Human factors
- Desires
- Trust relationships
- Behaviours
- Expectations
- Biases
- Abilities
- Roles
- Relative importance
- Unknown unknowns.

For a list of some stakeholders, please see the list in our August 2018 ONdrugDelivery article.[1]

IDUSTRIALISATION IN NEW INDUSTRIES IS NOT NEW

Henry Ford made the automobile an affordable "necessity rather than a luxury". He fought off an association that tried to bankrupt his fledgling company by speciously claiming that Ford infringed a patent controlled by the association. Ford himself patented some 150 inventions. While he was doggedly independent and held some highly controversial views, he industrialised automobile manufacturing with the scalable assembly line. The Ford Motor Company thrived while most of its 250 competitors in the 20th century disappeared. Alongside General Motors and Chrysler, Ford dominated the US automobile market until international manufacturers, such as Toyota and Volkswagen, disrupted the growth of the "Big Three" in the 1960s and 1970s.

In an obvious strategic move, Ford secured more than 2,000 patents by 2020, and has filed more autonomous vehicle patents than any other automaker. As of 2019, Ford led Google and Amazon in the number of patents held.

INNOVATION IN EXISTING INDUSTRIES IS NOT NEW

An example of a major innovation that we now see as a universal and foundational part of an industry is the use of automated product identity and data capture (AIDC), most commonly embodied as barcodes (Figure 2). Last century, in the 1980s to be precise, Walmart demanded that its vendors apply a universal product code (UPC) to the products they bought for sale. In 1983, Walmart began

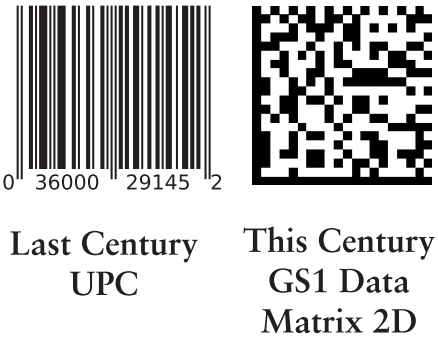

Figure 2: While it's almost unthinkable for a consumer product today to not bear a barcode, in the 1980s they were a revolutionary idea in the retail industry.

using UPCs as part of the checkout process and extended their use deep into its supply chain management. There was and is still no regulatory requirement for a barcode.

The entire retail industry followed. This led to tremendous changes in the availability of sales and supply chain information and massive savings. Laws and rulemaking requiring AIDC on prescription drugs and many medical devices were introduced in the US in 2013. Manufacturers and distributors have largely implemented AIDC marking on schedules that have been pushed back several times – provider implementation still generally lags very behind. For example, the use of AIDC on some covid-19 related products was delayed to allow faster fielding.

More on Walmart as a Potential Disruptor

Today, Walmart remains the largest retailer by sales volume in the US (there will be more on the second largest US retailer later in this article). From this position, Walmart is looking to break into the healthcare industry.

In late June 2020 Walmart announced the introduction of a generic private brand insulin made by Novo Nordisk. Furthermore, since opening its first clinic about a year ago, Walmart has announced plans for at least 20 more. Walmart has formed relationships with Clover Health and Humana. Then, in June 2021, Walmart Health was announced as the company's healthcare division, thanks to the acquisition of telehealth provider MeMD.

AIDC can be a tool for Walmart or other disruptors. By providing better patient information, a disruptor could help to ensure compliance and adherence, prevent the need for product returns, keep the supply chain secure and reduce the overall cost of healthcare.

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"Pharma firms are fastidious in filing patents on their compounds. However, in some companies, recognition of the importance of patents related to drug delivery devices sometimes seems to be seen as lower priority than it ought to be."

PHARMA IS A WELL-ESTABLISHED INDUSTRY WITH A HISTORIC FOCUS ON INTELLECTUAL PROPERTY

Patents are clearly an essential strategic element in the pharmaceutical industry's historic successes. Pharma companies often file patent after patent to extend their period of exclusivity. Manufacturing, marketing, sales and other functions execute on key innovations, but it is IP, not manufacturing expertise or marketing muscle, that enables the industry's hefty gross profit levels. Accordingly, pharma firms are fastidious in filing patents on their compounds. However, in some companies, recognition of the importance of patents related to drug delivery devices sometimes seems to be seen as lower priority than it ought to be.

Patient drug delivery management will provide information on efficacy and safety. Data about medications in patients' hands has moved beyond "nice to have but too complicated and expensive to bother with except in clinical trials." Drug delivery management and the data derived from it are now drivers of value.

Amazingly, the zest to build patent walls on drug delivery data has somehow been seemingly overlooked by much of pharma. Research on forward citations for some drug delivery patents indicates that drug delivery management "sorta snuck up on many large pharma companies". The march towards drug delivery management has been quickened to double time in the US by high pharma product costs, demands for real-world evidence of the value of improved outcomes, new regulatory requirements for lifecycle management and the recognition that data is essential to corporate performance. The technologies are in place for the disruption of the legacy healthcare pharma, provider, distributor and payer industries. Self-disruption is a possibility.

A new sub-industry of contract developer and manufacturing organisations (CDMOs) has been built around pharma's need for outside expertise in electromechanical medical devices capable of data capture. Over some years, CDMOs have been vertically integrating to fulfil pharma's needs. In some cases, CDMOs have filed patents on devices and systems to then licence their IP to pharma customers.

Fundamental changes to drug delivery management data will likely disrupt legacy systems by offering patients and society better pharma outcomes. The resultant changes may offer healthcare practitioners freedom from some of the bureaucratic legacy practices – we can hope. Delivery device and data technology IP can serve to build new or augment existing proprietary pharma positions.

A venture capitalist friend said "IP is rarely a wall, but a creative assembly of bricks to maintain legitimate pharma monopolies devolving from high-risk, high-capital R&D." Patents covering data retrieval from smart connected combination products is a valuable brick in this wall – and a brick through the window of legacy thought. Automated identity enables:

- Product control
- Dissemination of drug and device product information
- Digitisation to generate real-world data for analysis and conversion into real-world evidence
- Understanding the effect of human variables following the stability, exposure and sensitivity of biologic products
- Tracking versions of software in or associated with drug delivery systems and medical devices.

These and other requirements argue strongly that healthcare should make AIDC part of its industrialisation efforts.

ONE OF THE MANY OTHER POTENTIAL DISRUPTORS EMPLOYING DRUG DELIVERY DATA

Global Healthcare Exchange (Louisville, CO, US), or "GHX", states that its services have enabled better patient care and billions of dollars in business processes savings for the healthcare community. GHX claims to be the world's largest digital trading network for healthcare data, bringing in US$1 billion (£730 million) per year for the 4,100 US providers and 600 suppliers that contract for its service. In a blog post,[2] GHX announced its plans to support moving patient care outside of traditional care sites even to patient homes.

In an article for Health Data Management, Chris Luoma of GHX explored how the supply chain can support this change.[3] Contracting and procurement have seen progress with standardisation and technology systems that generate data to support strategic sourcing.

GHX may also look to comparing outpatient versus in-home administration of medications. GHX and many other companies have filed multiple patents related to connected drug delivery to support the shift towards favouring at-home self-administration by patients over the traditional healthcare practitioner-based in-clinic model.

Pharma drug delivery management technologies can save lives and enhance patient quality of life. Value for pharma products can be enhanced and demonstrated by connectivity technologies and IPs that help to ensure improved outcomes. The question is: Who will be the first to really break through and make use of connectivity to gain real-time information and disrupt the current drug delivery industrial norms?

DATA IS NOT PATIENT SUPPORT, TRAINING OR EDUCATION

Drug delivery includes, or should include, patient and caregiver support, training and education. The gaps in the current

"GHX and many other companies have filed multiple patents related to connected drug delivery to support the shift towards favouring at-home self-administration by patients over the traditional healthcare practitioner-based in-clinic model."

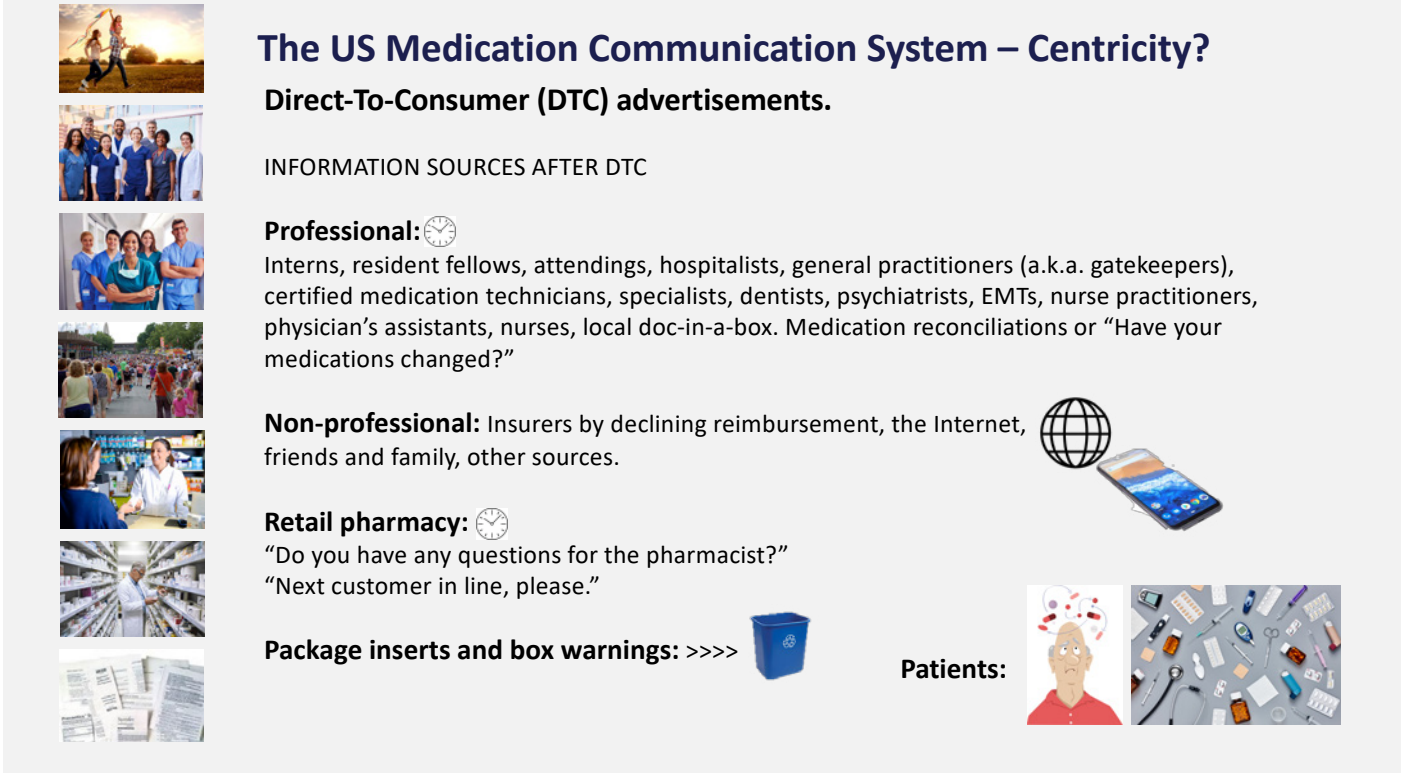

Figure 3: Information sources for patients in the current US healthcare industry.

information supply norms shown in Figure 3 are obvious to patients and, until somewhat recently, that was all that was offered. Patients were not usually well informed about the drugs that they were prescribed.

For many insured patients, drug costs have not been a significant factor in their relationship with their medication regimes. However, newer drugs are often more expensive, the media and legislators have emphasised drug costs, fewer patients have employer-provided insurance coverage and insured patients are now often required to pay a greater share of their pharma expense than in years past. New drugs have been approved for previously unidentified diseases that affect smaller populations or for conditions that have thus far been treated by less-effective drugs or left untreated altogether. These facts have driven a greater desire in the patient population for pharma information, which, coupled with the ready access to consumer information in other sectors, has led to the situation now where pharma must increasingly deal with patients/payers who have come to expect instant gratification of their desire for product information.

Some not-for-profit consortia, such as GTMRx (Tysons Corner, VA, US), are proposing better systems. Others are lobbying for legislation to empower patients. Also, many drug price comparison companies have now entered the US market, with GoodRx (Santa Monica, CA, US) being a leading example. Further industrialisation in pricing data supply is coming and disruption from various commercial entities, including diagnostics providers, is underway. One way to offer greater patient value for a treatment is for it to include more features for the patient.

> "2020 was a banner year for pharma and other healthcare, hospital and insurance industries in total expenditures on advertising and lobbying. Patient and consumer groups remained far behind in funding their efforts."

Even though pharma has invested in patient support programmes, including payment assistance programmes, patients' use of them is very limited. Patient payment assistance is usually advertised as: "If you cannot afford your medication, pharma company X may be able to help." However, 2020 was a banner year for pharma and other healthcare, hospital and insurance industries in total expenditures on advertising and lobbying. Patient and consumer groups remained far behind in funding their efforts.

Investing in digital and personalised consumer (patient) communications and consumer satisfaction (including patient outcomes and loyalty on the part of patients and other stakeholders) is a medium- and long-term strategy that can maximise both corporate value and patient outcomes. Such investments are different from environmental, social and governance (ESG) investing, which is criticised in the US as being ineffective, misplaced, elitist and "woke".

Pharma has done a remarkable job of identifying, scaling up and distributing covid-19 vaccines in response to the current global pandemic. However, failure to provide effective patient support, training and education on drug delivery can lead to:

- Unfilled prescriptions
- Failure to follow protocols
- Reduced efficacy
- Poor patient outcomes
- Emergency service overuse
- Unnecessary hospitalisations and deaths
- Wasted expenditures.

Effective patient support, training and education for the covid-19 drug delivery effort was missing to date in many countries. Now is the time to prepare to help patients end the current pandemic and respond to the next pandemic event.

INDUSTRIAL HUBRIS CAN BE DISASTROUS AND COSTLY

Volkswagen of America introduced the luxury Audi 5000 in 1978. The marketing slogan "Audi – The Art of Engineering" was used to differentiate the brand and Audi 5000 sales rose significantly over the years. With increasing sales came increased consumer complaints of unexpected sudden acceleration when shifting from "park" to "drive" or "reverse". Complaints included some accidents and fatalities.

For years, Volkswagen of America denied that the car was defective and blamed inexperienced, or even "short", drivers for the accidents. In 1987, after five recalls, a number of design changes and a public relations blame storm, Audi 5000 sales and Audi sales overall had declined by more than 50%. The Audi 5000 name was dropped in 1988.

The Boeing 737 and its variants was the bestselling line of commercial passenger planes until 2019. The 737 MAX was rushed into service in May 2017. The MAX suffered recurring failures of its automated flight control systems, which were eventually found to have contributed to causing two fatal accidents. A lack of costly pilot training probably contributed to the accidents.

The MAX was subsequently grounded worldwide from March 2019 to November 2020. Investigations indicated a cover-up of known defects by Boeing and lapses in the certification process by the US Federal Aviation Administration (FAA). After being charged with fraud, Boeing paid settlements amounting to more than $2.5 billion. In late 2000, the FAA cleared the MAX to resume service, subject to mandated design and training changes.

However, about six months after the MAX was cleared to fly again in the US, a potential electrical problem caused renewed grounding of more than 100 737 MAX planes and a suspension of MAX deliveries. Boeing's 777X and 787 Dreamliner, originally scheduled for 2019-2021 deliveries, and the new Air Force One, are far behind schedule. Airbus has since taken the lead in passenger plane sales.

The reported financial costs of these types of hubris are high. Non-financial costs are difficult to calculate and are probably even higher. Listening to and adopting different approaches to customer, driver, pilot and engineering support education and training might have mitigated damages.

PATIENTS AS CONSUMERS – AND THOSE WHO SERVE THEM

The big tech companies, such as Amazon, Apple and Google (Alphabet), "get" the consumer desire for information. These and other companies have built their success off consumer desire for convenience, online access, competitive pricing, information, support, education and training. Amazon's subscription model, one-click shopping, preferred product selections, verified purchase reviews, personal order history and "customers also bought" features all readily provide information to consumers. Apple's "Genius Bar" and Google's assisted intelligence have changed the retail, publishing and online search industries. These companies and others provide tools, assist their customers and use their informatic tools to extend the functionalities of their supply chains to end users, vendors and other stakeholders.

Patient and caregiver reliance on internet-based information for most products is not as restricted as it is for pharmaceuticals. While the US allows direct-to-consumer advertising, there are still restrictions on what can be said in internet-based information. Patients, however, can say what they want, leading to the idea of "ask your doctor". Ask your doctor is being supplemented by corporate offerings of information and "voices of patients" online. As with other social media, these voices are changing the amount and content of drug delivery information and influencing a change in drug delivery models. Pharma, payers, practitioners, regulators and others are coming to rely more on patient input well beyond the clinical trial.

> "As with other social media, these voices are changing the amount and content of drug delivery information and influencing a change in drug delivery models. Pharma, payers, practitioners, regulators and others are coming to rely more on patient input well beyond the clinical trial."

> "Legacy companies may struggle to prevent Amazon and others from making their presence known as the disruptors move into the sector."

AMAZON AS A POTENTIAL DISRUPTOR

"Brick and mortar" retail booksellers were quite complacent when Amazon first began selling books in 1995. Amazon disrupted publishing and then much of retail distribution by providing customer choice, guaranteed satisfaction, service and information. In short – competition, which it provided on a massive scale. Amazon is now the second largest US retailer by sales volume (Walmart still holds the top spot). However, the changes introduced to the industry by Amazon were not without a darker side for some competitors and present a potential broader risk if abused.

Legacy companies engaged in drug delivery may now be trying to avoid similar disruption. New entrants and new combinations in drug delivery are worrying legacy stakeholders. Legacy companies may struggle to prevent Amazon and others from making their presence known as the disruptors move into the sector. Amazon, for example, has:

- A greater capacity for collecting and analysing data than many existing healthcare stakeholders combined
- Massive capital reserves
- A deep and through understanding of the US consumer market
- Know-how on gaining value through customer centricity
- The ability to synthesise a range of information to serve its customers both profitably and conveniently
- An extensive knowledge of US law

- Experience with a wide variety of vendor relationships
- An appetite for growth in the healthcare industry
- Independence.

A few of Amazon's potentially disruptive entries into "healthcare without walls", including telemedicine, are:

- In 2018 Amazon bought PillPack (Manchester, NH, US), which already held licences to distribute pharmaceuticals in 49 states. Publicly listed pharmacy companies took a hit to their stocks on the day Amazon announced the PillPack purchase.
- In November 2020 Amazon announced Amazon Pharmacy, which offered discounts of up to 80% on generic and brand-name prescription drugs to patients if they forgo using insurance. This being on top of its already substantial over-the-counter pharma offering.
- In 2020 Amazon began building covid-19 testing capacity for its employees. The test has been cleared by the US FDA. Diagnostics are essential to home health.
- In August 2020 Amazon introduced the Halo fitness tracker. Like Amazon Prime, Halo has a recurring fee. Halo has some features not available on the Apple Watch.
- In February 2021 Haven, the joint healthcare venture among Amazon, Berkshire Hathaway and JP Morgan Chase, was ended. Amazon learned from the experience.
- Amazon Web Services (AWS) promotes partner organisations, such as Murj (Santa Cruz, CA, US, which offers cardiac device care; Redox (Madison, WI, US), a digital health platform company; and others.
- In early 2021 AWS announced a four-week accelerator programme open to digital health start-ups, assisting them by enabling collaboration with Amazon experts and their healthcare customers and partners. The programme is targeting paediatric and adult patients.
- Amazon has now signed up multiple employers to its in-house healthcare service, Amazon Care, a virtual health service benefit as part of the national expansion of its employee health service.

The readers of ONdrugDelivery will be key in deciding who will innovate, who will lead, who will disrupt and how further industrialisation of drug delivery will evolve.

ABOUT THE COMPANY

In the area of drug delivery, New Directions Technology Consulting is the exclusive market developer for the mMed patent portfolio. Medication telemanagement systems based on the portfolio can be used to develop innovative health and wellness programmes.

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ABOUT THE AUTHOR

Napoleon Monroe, the sole inventor of the mMed medication-telemanagement patents, has been involved in the successful commercialisation of patents for decades. He spent more than 20 years at Survival Technology (now part of Pfizer), where he built up and managed its IP portfolio. There, he invented three medical devices that were patented and commercialised – two for autoinjectors and one for a transtelephonic peak-flow monitoring device. Mr Monroe also led teams that invented, prototyped, tested, commercialised and scaled up emergency pharmaceutical delivery systems, such as the original EpiPen, for treatment of anaphylactic shock, and the Antidote Treatment Nerve Agent AutoInjector delivery system, which still protects US and allied military and civilian personnel.

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SHL MEDICAL

DEVELOPING A FULLY AUTOMATED MODULAR MACHINE PLATFORM FOR AUTOINJECTOR TESTING

In this article, Lucy Chung, Senior Director, Automation Systems, and Gilbert Fluetsch, Senior Director, Automation Systems, both of SHL Medical, discuss the benefits of a modular automated test platform.

Modularity is not a new concept in manufacturing. From cars and furniture to computers and software, products created using a modular framework are ubiquitous, and the benefits of a modular approach in design and manufacturing are well documented – particularly faster development, lower cost of goods, increased output and more flexible design options. However, in the pharmaceutical industry modularity only began to gain traction in the past 25–35 years in the form of modular bioprocessing production facilities.[1] The key driver behind this adoption of modular manufacturing has been the shift from producing a single, blockbuster drug to instead producing a series of targeted therapies, which calls for smaller batches with lower costs and faster development.[2,3]

As more pharmaceutical companies seek device solutions that can meet these new requirements, the impact of this shift is also evident in the drug delivery device industry. Over the past decade, preconfigured or platform products have been increasingly sought after due to their ability to offer faster turnarounds and lower costs with the use of common machinery and toolsets. Yet with rising competition in the space to launch biosimilar drugs, which often require customised designs for brand differentiation and usability requirements, devices are increasingly expected to offer flexibility beyond the confinements of a platform product.

MODULAR EQUIPMENT FOR AUTOINJECTOR DEVELOPMENT

In a 2020 article outlining the application of modular design thinking in autoinjector development, SHL Medical discussed how modularity offers the opportunity to leverage all the advantages of traditional platform device technology (e.g. in speed, cost and pre-set designs) while still allowing for various customisations in the device's design and development models.[4] The result is a flexible device platform that can meet the requirements for industrial design customisation and production scaling. These competitive advantages also apply to the automated equipment strategy for autoinjector assembly and final device testing.

Automated manufacturing refers to the design and application of a system that enables automatic processes in the production stream of device development. Integrated with computer-aided manufacturing (CAM)

> "A modular equipment platform uses a common base infrastructure that can be adjusted to process a mix of different products – or several versions of the same product – at speed, on a flexible scale and with consistent quality."

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systems, automated machines offer a more efficient and cost-effective means of mass production. In most cases, these platforms are built for single blockbuster products that use dedicated manufacturing set-ups to lower the overall cost of goods. By contrast, a modular equipment platform uses a common base infrastructure that can be adjusted to process a mix of different products – or several versions of the same product – at speed, on a flexible scale and with consistent quality.

Besides the shift from blockbuster products to personalised treatments, this additional level of flexibility beyond high-volume production is also being driven by the nature of the pharmaceutical and medical device industry. Before a combination product is approved and launched on the market, it goes through numerous phases, including usability studies, clinical trials, pilot market testing and even sample requests from regulatory bodies for feedback and approval, all of which require different production volumes. Furthermore, as the product progresses through the different phases of its life cycle, forecasts and orders might also need to be scaled up or down to reflect changing market demand.

BENEFITS OF A MODULAR AUTOMATED TESTING PLATFORM

SHL Medical's in-house automation services are led by the automation systems department. The team has over two decades of experience designing, developing and building a wide range of manual, semi-automatic and fully automatic machine systems for autoinjector assembly, final assembly and final device testing.[5] The majority of these systems are custom-built for single device projects for use internally or by SHL customers at their local sites. To put this into perspective, SHL has shipped more than 360 sets of assembly and test fixtures and equipment to 40 companies in 16 countries across Europe, Asia and North America.

SHL first developed a highly flexible and fully automatic testing machine (FATM) in 2017 after foreseeing the need to create a universal testing machine featuring flexible mix-and-match testing options for both syringe-based and cartridge-based injection devices. To achieve this, the company applied the modular design concept to its well-established FATM infrastructure, drawing on its years of experience developing automated testing machines for a diverse scope of injection device projects.

The result was a universal testing platform featuring interchangeable tools and fixtures for increased device compatibility. The platform also has a modular machine base that can be arranged and expanded for different test stations, as well as an integrated software program that simplifies the customisation of test sequences.

In addition to increased flexibility and versatility for devices and testing items, other key benefits enabled by the modular FATM include:

- Faster turnaround for testing equipment development
- Lower costs through investment in tools and fixtures as opposed to entire lines of machinery
- Increased testing efficiency with automated processes
- More stable testing quality due to fully automatic handling
- The opportunity to scale production up (or down) for product lifecycle management
- The ability to introduce incremental upgrades
- Reduced equipment downtime
- Reduced overall carbon emissions per device by maximising the reuse of machine tool frames.

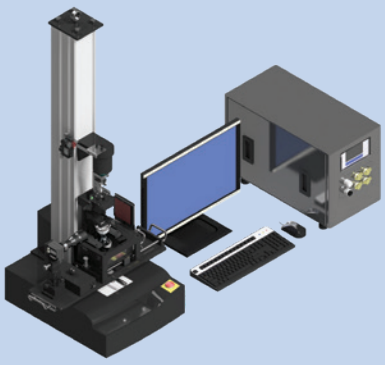
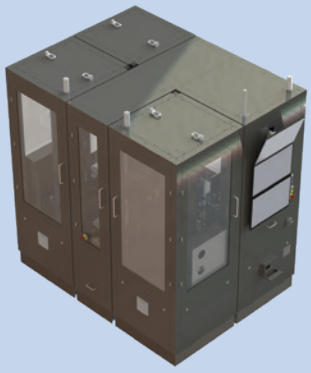
Type	Manual testing machine (MTM)	Semi-automatic testing machine (SATM)	Fully automatic testing machine (FATM)
Image			
Description	Integrated system with interchangeble tools	Modular SATM station with interchangeble tools	Modular FATM platform with interchangeble stations
Key benefits	• Used in laboratories and for final testing • Suitable for products in development phase • More freedom to configure testing items • Tools can be easily configured to be compatible with multiple universal tester brands.	• Used for final testing • Suitable for platform products at various stages of development or in mass production, as well as for customised products in mass production • Enhanced stability due to automated processes • Easy to learn and maintain • Reduced test time.	All the same benefits as SATM with the addition of: • Easy to set up due to fully integrated, user-configurable software system • One-time equipment/software set-up for multiple test items • Faster development compared with building new, fully customised machines.

Table 1: Overview of testing machines.

Before the introduction of the modular FATM, each new testing machine had to be customised for every new device project based on its individual design, test parameters and output requirements (Table 1). With the introduction of a modular machine base, however, semi-automatic testing machines (SATMs) can now be developed as standalone test stations that can work independently or be assembled with other stations to form a customised test sequence.

By supporting the flexibility to mix and match different test stations, the modular FATM platform enables new test sequences to be arranged according to each product's requirements.

For example, a two-step, syringe-based autoinjector such as SHL Medical's Molly would require the simulation of two main actions: a pulling motion to remove the cap and a pushing motion to activate the injection. Meanwhile, a cartridge-based autoinjector that requires the user to shake and mix the drug prior to injection would involve a more complex series of test sequences, as illustrated in Figure 1.

> "When a unique test condition is required, such as shaking to simulate the drug product's actual handling, an additional station can be added and programmed into the test sequence."

THE LEGO-LIKE APPROACH TO MACHINE MODULARITY

Despite the difference in test sequences, the same test items – such as cap removal force, injection activation force and injection test – could be tested on the same machine base wherein specific tools, such as grippers, holders and nests, can be swapped out for different devices. Furthermore, the software can be easily configured to define the intricacies of the test sequences. When a unique test condition is required, such as shaking to simulate the drug product's actual handling, an additional station can be added and programmed into the test sequence.

This ability to endlessly combine various elements to create "new" equipment can be best understood through Lego bricks – one of the world's most recognisable examples of modular design.

Modularity is impossible without some level of standardisation. Much like how Lego bricks can be combined and taken apart, individual machine stations are designed to be mutually compatible so they can be disassembled and reassembled.

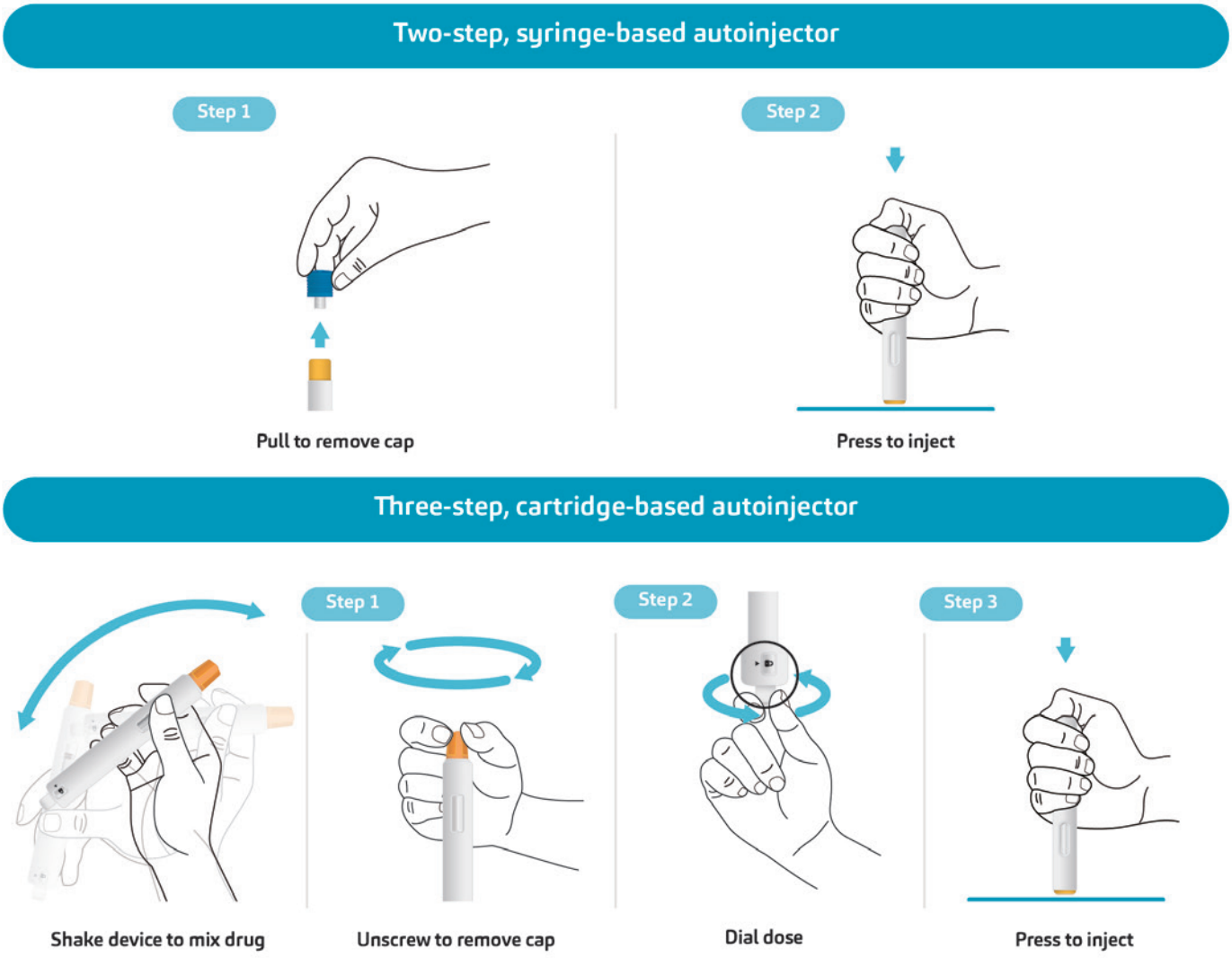


Figure 1: A simplified comparison of the test items for a syringe-based autoinjector and a cartridge-based autoinjector requiring mix before use. Other available test items, such as needle length, injection time, dose accuracy and needle cover override force, are not outlined.

This standardised design serves as the framework within which flexibility is achieved (Figure 2).

Another key factor facilitating the system's modularity is the addition of a robot arm. To accommodate the various add-on stations, a tailored control system was designed so that the robot arm can be easily set up to perform motions of various levels of complexity. To this end, SHL challenged its software engineers to extend the robot arm's capacity beyond conventional pick-and-place functions to include capabilities such as loading and dispatching trays as well as safely removing glass beakers filled with liquid solutions and replacing them with empty containers before continuing the test cycle (Figure 2).

The difficulty for the engineers lay not just in characterising complex and intricate motions while avoiding hardware collisions but also in identifying all possible motions and integrating them into a single software system that could allow users to configure a complete test sequence with relative ease on the FATM's human-machine interface. This user-configurable software system – which addresses a large number of possible use cases, each with their own configurable elements and settings – is what enables the Lego-like equipment stations to function as a fully automated modular autoinjector testing platform.

In a 2020 article, SHL discussed applications of deep learning in automated assembly machines.[6] Deep learning has also been incorporated into the FATM's robotic system to help further increase its flexibility. Specifically, SHL combined a visual guiding inspection system with deep learning capabilities for use at the outset of testing activities, namely the first step of picking up an autoinjector for further processing.

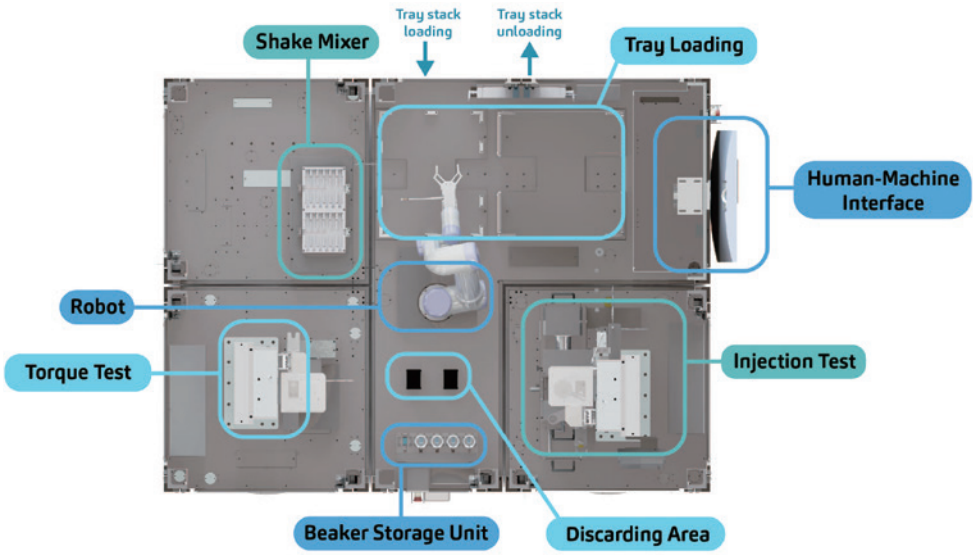


Figure 2: Top-view layout of a modular FATM for a cartridge-based autoinjector. Modular bases consisting of different test functions are assembled similarly to Lego bricks.

> "Autoinjectors do not need to be perfectly positioned in a designated area for the robot arm to be able to initiate the testing process."

A subset of machine learning in artificial intelligence, deep learning can mimic the human brain to detect objects and recognise shapes without the need for explicit data sets. It allows the robot arm to "teach itself" to distinguish the autoinjector's features and automatically adjust its movements and trajectory in relation to the device's positioning inside the tray (Figure 3). In comparison, a traditional control system would require the input of extremely specific instructions, such as length, width, colour and precise position, in order for the robot arm to accurately identify the object and move according to the predefined trajectory. In practical terms, this means autoinjectors do not need to be perfectly positioned in a designated area for the robot arm to be able to initiate the testing process.

While this may seem a trivial task to assign to artificial intelligence, it in fact encapsulates the myriad benefits of modular FATMs outlined earlier. For example, autoinjectors of different shapes and sizes can be placed in trays that can themselves be of varying dimensions. With the system's ability to learn and self-adjust to different device and tray parameters, developers no longer need to build separate equipment or fixtures for every device project that comes through their doors. This flexibility is paramount as it significantly enhances FATMs' compatibility, enabling them to support autoinjectors with various industrial designs.

Figure 3: Side-by-side view of the tray and robot arm (left) and a screen capture from the artificial intelligence system (right). Through the integration of deep learning, the robot system can recognise unique device features and automatically adjust its movement in relation to the positioning of the devices inside a tray.

> "By reusing much of the machinery to test different injection devices, emissions from producing and operating individual pieces of machinery are reduced, increasing the overall sustainability of the final product."

THE FUTURE OF AUTOMATED TESTING

A modular equipment architecture, by definition, uses a common infrastructure that can be adjusted and reused for a variety of products. By reusing much of the machinery to test different injection devices, emissions from producing and operating individual pieces of machinery are reduced, increasing the overall sustainability of the final product.

Even though the syringe and cartridge autoinjectors shown in Figure 1 have vastly different device features and handling steps, they share approximately 60% of the modular equipment units when comparing their respective FATM set-ups. Looking further into the interchangeable parts, internal data also shows that the vast majority of the machine structure is reused, meaning that the effort and raw materials needed to assemble a modular testing machine for an individual product are also significantly lower than those needed to build a new machine from scratch for the same purpose. Of course, these are general observations, and different projects may yield different data.

While further research is needed to elucidate the precise carbon impact of a modular FATM on a product's lifecycle, SHL will continue to refine its modular approach in both device designs and equipment strategies in order to fully realise the benefits that modularity presents to its customers and the broader community. As part of this commitment, the company has launched an industry-leading initiative aimed at enabling container-free testing for the fully automated modular machine platform. With this forward-looking initiative and others like it, SHL is taking concrete action to enhance its automation services and stay ahead of the demands of the drug delivery industry.

ABOUT THE COMPANY

SHL Medical is a world-leading solutions provider in the design, development and manufacturing of advanced delivery devices, such as autoinjectors and pen injectors. It also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL has successfully built a strong international team of experts that develop breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injection systems that can accommodate high-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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ABOUT THE AUTHORS

Lucy Chung is a director in SHL Medical's automation systems department (AMSD), where she is responsible for overseeing equipment design, development and manufacturing, as well as overall production quality. As one of SHL's first five employees in Taiwan, Ms Chung was instrumental in establishing the company's stringent product testing and quality systems. She previously held roles in project management, operations and customer service in AMSD, and in 2004 helped develop the semi-automatic testing machine for SHL's first autoinjector product, DAI. Ms Chung has a BSc in Industrial Engineering from the National Taiwan University of Science and Technology.

Gilbert Fluetsch joined SHL Medical's automation systems department in early 2016. His responsibilities include leading the engineering teams, standardising the existing equipment portfolio and overseeing the development of high-speed assembly and testing machines. Prior to joining SHL, Mr Fluetsch served for almost three decades in leading engineering, operations and sales management roles in the medical device and semiconductor industries. He was the vice-president of sales and marketing for Ismeca Europe in Malaysia from 2007 to 2010 and held key account management positions at several US-based automation companies between 2010 and 2016. Mr Fluetsch has an MBA in High Technology Management from the University of Phoenix (AZ, US) and a BSc in Business Administration from California State University San Marcos (CA, US).

HOW DIGITISATION IS DELIVERING COMPETITIVE ADVANTAGE IN DEVICE ASSEMBLY

In this article, Jens Schou Christensen, Assembly and Packaging Head of Product Management, and Sebastian Berninger-Lund, Assembly and Packaging Automation Chief Designer, both at Stevanato Group, present the business case for the wider implementation of digitisation and the greater use of data to deliver assembly line improvements.

It is suggested that by as early as 2040, smart home products will be adopted almost universally across Europe. So far, the pace of uptake in new technologies has been meteoric – in 1998 just 9% of UK households had internet access, whereas today the figure is more than 90%.[1]

This surge in demand for technology has transcended into the manufacture and assembly of drug delivery devices. Today, data and the digitisation of assembly equipment work hand in hand to deliver competitive advantage to pharma partners in terms of product quality, continuous improvement, de-risking maintenance and change management and, critically for the near future, the ability to deliver unique identities and traceability for every assembled device.

THE BUSINESS CASE FOR DIGITAL MANUFACTURING IS COMPELLING

Anyone working in drug delivery today will be very much aware of the advancements in connected devices and how the Internet of Things (IoT) is predicted to make a huge impact on patient adherence, as well as saving the whole healthcare industry billions of dollars as patients, healthcare professionals, payers and pharma partners take advantage of the data created to improve therapies and how they are delivered.

> "While much of the industry focus has been on the development and market launch of connected devices, there has also been a quieter digital revolution in manufacturing and assembly, where the increase in complexity of pharma partners' requirements (including more personalised medicines, the ever-evolving regulatory landscape and cost) has caused production facilities to look again at the use of smart manufacturing technologies."

While much of the industry focus has been on the development and market launch of connected devices, there has also been a quieter digital revolution in manufacturing and assembly, where the increase in complexity of pharma partners' requirements (including more personalised medicines, the ever-evolving regulatory landscape and cost) has caused production facilities to look again at the use of smart manufacturing technologies.

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A recent white paper from Bain & Company predicts some game-changing improvements following the implementation of digital manufacturing. Smart connected factories are estimated to produce savings of 20% or more, with a 14% increase in delivery reliability. There is also forecast to be a 17% reduction in costs related to poor quality and a saving of 15% in the cost of converting raw materials into drug products.[2]

For a few years now, some delivery device solutions providers have advocated the increased use of digitisation to deliver data-led enhancements, not just to monitor and improve product quality but also to drive overall equipment effectiveness (OEE), deliver predictive maintenance and use machine learning to continuously improve processes.

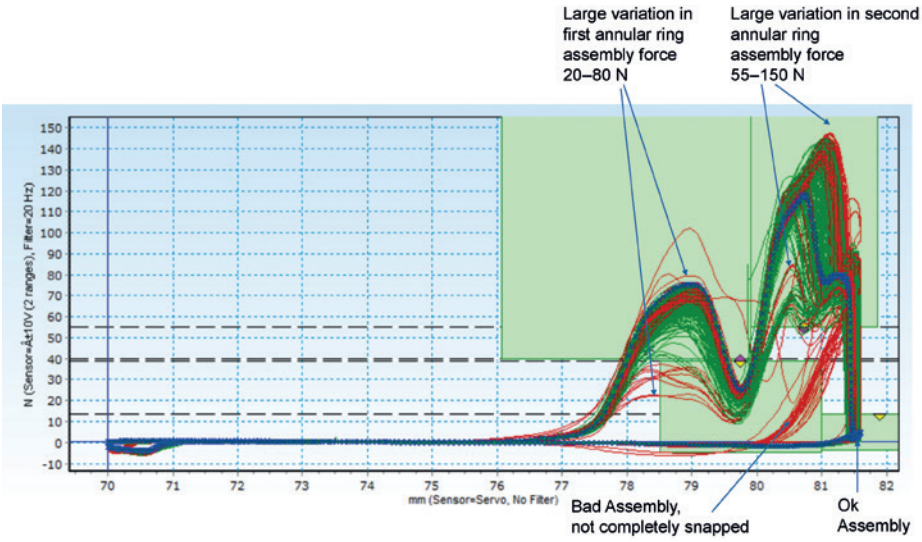

Figure 1: An example of data measuring an assembly process and driving improvements in performance – raw data (snap).

USING DATA TO DELIVER QUALITY AND COST IMPROVEMENTS

The use of data to drive any kind of improvement is not a revolutionary idea, for example Six Sigma has been around since the mid-80s. However, in a recent survey conducted by Stevanato Group, 10% of respondents to an online study stated that no data was collected from their production operations, and an overwhelming 74% were only using data in a limited capacity to drive quality improvements, mainly in product quality, OEE and predictive maintenance. These respondents came from a range of functions within the pharma and life science industries.

Stevanato Group has been researching the positive impacts of a data-based quality checks, compared with visual or semi-automated checks. The company has noted the benefits both in terms of cost reduction and quality improvement. From a cost perspective, each machine is more productive due to fewer interventions during manufacture. While more or less the same number of validation systems are still required, manufacturing space has been optimised as fewer inspection stations are needed. Because the parameters for quality have been established, many problems can be addressed agilely in-line. In turn, the company is witnessing the need for a reduced overall manufacturing footprint and greater OEE.

> "Historically, actions such as root cause analysis would have taken many hours, a great deal of intellectual energy and costly iteration. Today, data, combined with expertise and experience, can effect big changes in performance in comparatively short timescales."

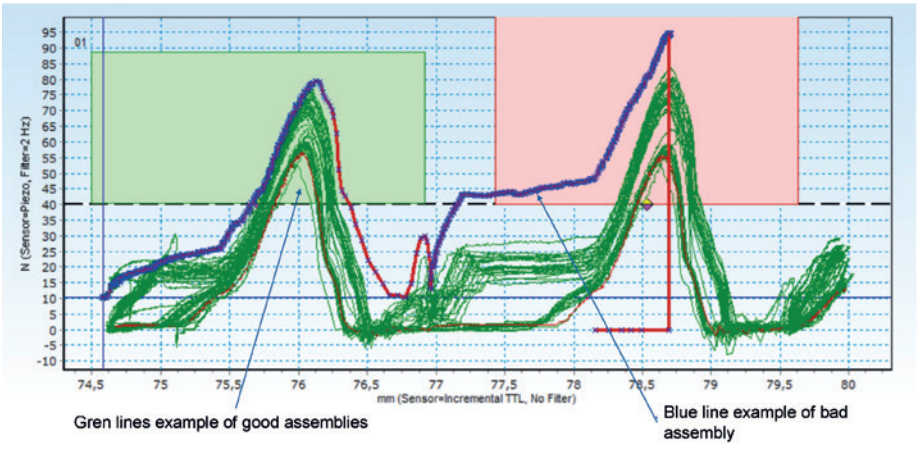

Figure 2: Showing how data-driven quality checks can reduce risk through effective and accurate measurement – example on raw data (click).

In terms of product quality, the data enables the company to optimise product design, validate the process and recognise "hidden" anomalies to detect the root causes of any quality issues. This process creates an holistic cycle of continuous improvement, with data always circling back to improving product design and overall quality.

The data in Figure 1 demonstrates how the snap process of two annular rings can be analysed. The x axis indicates the position of the gripper, with the y axis showing the force implemented for placement. The measure is to establish if the anticipated forces needed for the snap of the two components matches what is, in reality, needed to engage correctly. The green lines mark items assembled correctly, with the blue line representing the average and the red lines showing incorrectly assembled components. The curves of the green lines can be seen to follow the correct path, entering the left-hand green box before descending into the lower box and then rising again into the upper green field on the right.

Figure 2 demonstrates a similar methodology, but in this case, instead of a linear movement, rotation is measured using

torque. Without such a system, a rotation would be made to deliver an expected number of clicks, however, we can now actually measure that all the clicks were done and make the set point the number of clicks rather than the amount of rotation.

USING DATA TO DRIVE ASSEMBLY PERFORMANCE

There is no better analogy for the state of play in device assembly today than the iceberg. While due diligence is given to key performance indicators (KPIs), much of the performance under the surface is not enhanced or even captured, leaving much room for improvement.

Stevanato Group's philosophy is simple – you cannot improve what you cannot measure, and you cannot measure what you cannot see. As such, the first step in driving assembly performance is to go beyond the KPIs – going below the water line to capture and store all the data possible. Stage two is about finding new ways to optimise performance – deep diving into why events occur, and where to look for the root causes of poor performance.

One example is the novel ability to use video capture to identify the cause of defects. At any time, a user can double click into specific event data to access a video file of the last ten seconds of the process, enabling them to see what went wrong and when (Figure 3).

Historically, actions such as root cause analysis would have taken many hours, a great deal of intellectual energy and costly iteration. Today, data, combined with expertise and experience, can effect big changes in performance in comparatively short timescales.

> "Stevanato Group's philosophy is simple – you cannot improve what you cannot measure, and you cannot measure what you cannot see."

Stevanato Group has gone one step further and implemented machine learning – allowing its intelligent machines to find new ways to optimise processes, based on the data generated. The company also employs predictive maintenance tools, which use data to identify patterns in breakdowns and address them before they happen. One example is the installation of air pressure sensors – by monitoring the stability of air pressure and the reaction time of the sensors, patterns can be identified that may affect overall performance. This approach combines data with the experience and expertise of the company's engineers and delivers several benefits – business interruption is mitigated, shut down/maintenance days are reduced and overall cost minimised.

WHY YOU NEED A DIGITAL TWIN

For decades, industry was used to working with 2D drawings, and then, in the 1960s, along came 3D – a transformational moment. Now, thanks to Digital Twin, we can work in 5D. Digital Twin is best described as "a digital replica of a living or non-living physical entity." Integrating IoT, AI, machine learning and software analytics, Digital Twin is viewed as a game-changer in the simulation and emulation of mechanical and automated performance. Why a game-changer? Essentially, it is now possible to create, manipulate and iterate the whole assembly process digitally, and only when the perfect parameters for success are determined is an investment made in the physical model. The return on investment from such an approach is substantial – no more downtime, no more trial and error – right-first-time modelling.

In a recent customer study, Stevanato Group asked respondents about their experience level with Digital Twin. Just 4% are actively using an implemented Digital Twin in daily business, with a further 14% at early stages. A total of 72% of respondents currently have no experience of Digital Twin – something Stevanato Group is keen to address, given the game-changing metrics associated with it.

It is fair to say that the definition of Digital Twin is still open to interpretation, depending on personal and corporate perspectives. While Stevanato Group certainly sees it as a twin of physical entity, others see it as an umbrella for all kinds of engineering processes and tool improvements.

From a design perspective, it enables software and mechanical engineers to align and work in parallel without the ambiguity or misinterpretation often associated with written specifications. Software engineers can begin their processes much sooner and programming time can be reduced as a result of the early alignment with mechanical engineering functions. As a result, this design solution is much easier to implement and can be reviewed by the customer to ensure it replicates the physical machine experience as much as possible.

At the design review phase, the Digital Twin can aid the selection of the right assembly concept from day one. Using animated design instead of 3D design to interrogate better the configuration of the equipment (its location, interaction with other machines, etc) before it is manufactured, saving considerable time and cost over conventional methods of design review.

In terms of process, the Digital Twin can help engineers understand and analyse the process more deeply and make improvements more quickly. In addition, it is a very powerful communication tool to enable wider understanding across teams.

Digital Twin also brings benefits in many areas of production, particularly filling, where the imperative is to limit the amount

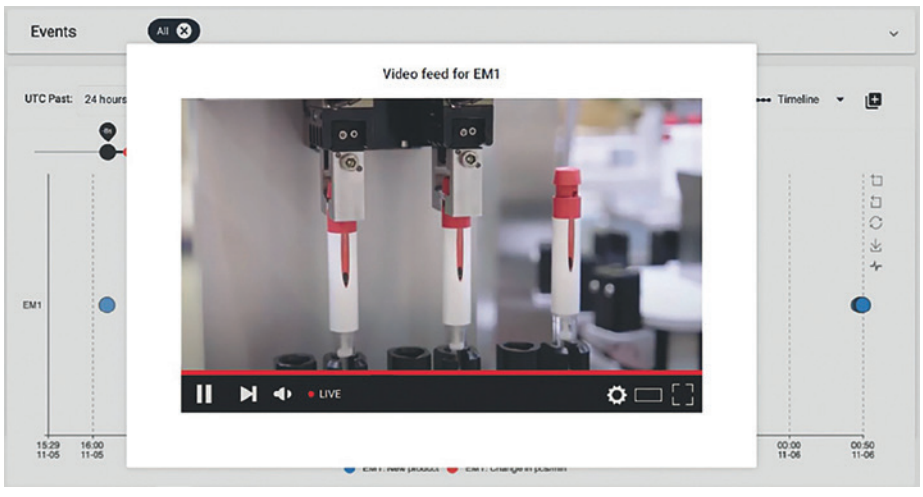

Figure 3: Live streaming of the process to establish cause of defects in quality.

"The advantage of digitisation is clear – extended data insight leads to more, and better, data. Using smart data enables design, development, validation and continuous improvement to happen in a comparatively low-touch yet high-impact way, without the associated business interruption costs of revalidating machines."

of people on the floor to reduce particulates entering the facility. Even by accessing the Digital Twin remotely, customers can quickly identify and resolve any problems, often without having to visit the production facility themselves.

The Digital Twin delivers benefits in terms of training and development too. The operator can use the Twin like the real machine, replicating the human-machine interface in a virtual environment. This enables the operator to interact with the products inside and outside the machine, and provide feedback in the design phase that will enable more efficient productivity in the final machine.

SOLVING A TWIN CHALLENGE FOR A PHARMA PARTNER

Stevanato Group recently participated in the successful delivery of a Digital Twin project in partnership with an automation group to support a pharma partner's pen injector assembly line. In this case, the client faced a twin issue – how to develop the assembly equipment at the same time as the product development was taking place. How to manage a design change on the product and, as a result, on the equipment was a key challenge. This twin issue was resolved using Digital Twin.

Right now, the project is installed and working, with the expectation that Digital Twin will deliver direct benefits in terms of reduced development time and cost, improving product quality and increasing OEE. There are anticipated softer benefits too in terms of providing a platform for training.

NOW IS THE TIME TO ACCELERATE YOUR JOURNEY TOWARDS INDUSTRY 4.0

It is no understatement to suggest that the healthcare industry is undergoing a transformative change. The pandemic has brought into sharp focus the need for more agile approaches to meet patient demand, at the same time highlighting the need for rapid scale-up in productivity while maintaining the integrity of the drug product.

Beyond covid-19, pharma partners are developing even more complex, specialised (and therefore expensive) molecules that require ever greater diligence in the quality of container. Personalised medicines create other challenges for assembly, where smaller batches with a greater level of serialisation will be needed. Lower volume batches do not sit comfortably with a pricing model predicated on high volume output, so the cost of production will become an even greater focus. All these considerations lead to the road towards the use of smart manufacturing technologies.

The advantage of digitisation is clear – extended data insight leads to more, and better, data. Using smart data enables design, development, validation and continuous improvement to happen in a comparatively low-touch yet high-impact way, without the associated business interruption costs of revalidating machines.

The net effect of this smart data is a highly optimised assembly function where process is improved, quality is enhanced, OEE is increased and unnecessary cost is mitigated.

According to Bain & Company, the biggest challenge in embracing this approach is integrating data, with 85% of pharma executive respondents citing effort as the biggest implementation issue.[2] The market influences driving digitisation are growing daily, and while there is no question there is an investment in hours required, with the right partner, the long-term benefits far outweigh the short-term efforts.

ABOUT THE COMPANY

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. The Group delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug life cycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

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ABOUT THE AUTHORS

Jens Schou Christensen is Assembly and Packaging Head of Product Management at Stevanato Group. In his role as Automation Technician and Engineer, Mr Christensen acquired broad hands-on and strategic experience in developing automation solutions for assembly and packaging equipment. With a passion for automation and the urge to push boundaries as key drivers, he has shaped innovative strategies and solutions in various complexities for Stevanato Group across two decades.

Sebastian Berninger-Lund is Assembly and Packaging Automation Chief Designer at Stevanato Group. Through his background in automation and project management, Mr Berninger-Lund gained fundamental experience to deliver quality and validated machines across high-technology industry branches. His passion for quality, structure and standardisation perfectly meets GMP needs, leading him to push Stevanato Group's product quality to new levels.

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ON drugDELIVERY

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Publication Month	Issue Topic	Materials Deadline
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October	Prefilled Syringes & Injection Devices	Sep 9, 2021
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December	Connecting Drug Delivery	Nov 4, 2021
January 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 9, 2021
February	Prefilled Syringes & Injection Devices	Jan 6, 2022
March	Ophthalmic Drug Delivery	Feb 3, 2022
April	Pulmonary & Nasal Drug Delivery	Mar 3, 2022
April/May	Drug Delivery & Environmental Sustainability	Mar 17, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
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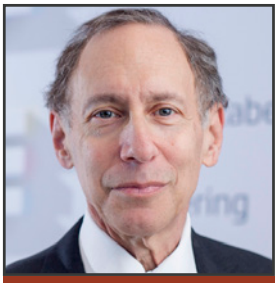

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PUTTING POST-PANDEMIC SUPPLY CHAINS TO THE TEST

In this article, John Swift, Head of Supply Chain at Owen Mumford, discusses the need for medtech companies to undertake a reappraisal of their supply chains in light of covid-19, taking into consideration how the pandemic has exposed vulnerabilities that have previously gone unnoticed or ignored.

The pandemic has forced many medical technology businesses to re-assess their supply chain in a short space of time. As companies struggled to address both peaks and troughs in product demand, it is likely that they identified stress points and vulnerabilities in supply chain infrastructure and operations. Throughout this pandemic, changing stress points have put companies under severe pressure, bringing supply chain risks to their attention, which could have caused issues at a future date.

It is now imperative to troubleshoot faults detected in supplier networks to ensure that businesses are protected from additional waves of the pandemic – or any other unexpected shocks in the supply chain. The pandemic has disrupted market dynamics, increased risks to long supply chains, reprioritised patient treatments and set up a forthcoming explosion of pent-up demand for postponed elective procedures. Failure in the medical device supply chain simply cannot be an option, as a lack of supply may impact the scheduling of future treatments and, ultimately, put lives in danger.

Any business continuity policy should comprehensively plan for operational continuity, disaster prevention and business recovery, in order to minimise the impact of disruptions on product supply. Within this framework, assessing supply chain risks must be an iterative process, where risks are mitigated as much as reasonably practicable within the agreed cost constraints of the business. It is true that, by definition, supply chain models come with risks. For instance, while the just-in-time model offers major benefits, such as reduced storage fees and much greater flexibility in inventory management, there is a very slim margin of error. A fresh look at the risks involved is well overdue.

> "Throughout this pandemic, changing stress points have put companies under severe pressure, bringing supply chain risks to their attention."

MANUFACTURING PLANTS

First, risk must be reassessed within manufacturing plants. There must be clear schedules and guidelines in place to check that manufacturing controls are working as expected. This could include a review of engineering spares policies, usage for all equipment and assets, and checking that service level agreements are in place where needed.

Each key process in the manufacture of medical devices must be reviewed in light of recent pandemic experiences. Are they still fit for purpose given what we have learned? Have risk parameters changed? Are new risk mitigation strategies required? Once this analysis is complete, the business needs to ensure that they are agile and flexible enough to respond to changes in customer demand. Additional investment may be needed here, for example in moulding or assembly capabilities across alternative or multiple sites, or in alternatively sourced materials.

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"Each key process in the manufacture of medical devices must be reviewed in light of recent pandemic experiences. Are they still fit for purpose given what we have learned?"

NEW PRODUCTS

Next, it is advisable to take a fresh look at products in development. The production and distribution model has to be built with initial launch requirements and subsequent scaling according to demand in mind. This will vary according to product; one scenario might be planning for a bespoke device design for individual customers (such as an autoinjector), while another case may be a platform design for multiple customers (such as a safety device for prefilled syringes) with an initially low volume but a forecasted growth to high volume. The business will therefore need to identify any potential risks to ongoing supply from initial launch, through product growth and into the projected demand. A sound scale-up strategy in line with forecasted demand will allow the business to make appropriate decisions related to tool investment, tool cavitation, assembly investment or transitions from low-volume engineered fixtures to full automation.

VULNERABILITIES

One survey of supply chain professionals in the medtech industry identified supply shortages (15%), lack of alternatives (12%) and delays in production (12%) as key post-pandemic concerns.[1] The polymer industry has not yet recovered from the effects of the pandemic, and downstream markets that use polymers (such as the medical device market) are experiencing longer lead times from suppliers and extended door-to-door shipping times for multiple routes and shipping lanes.[2] There are various reasons for these delays, including a surge in demand for plastic products (such as appliances), a global shortage of shipping containers and interruptions in production schedules.

Companies will need a broader and more rigorous tracking and management process to improve the quality of information about their supply chain, and to ensure that this information is as up to date as possible. The earlier they receive information on potential disruption to supply, the quicker they can implement mitigation activities to avoid or minimise impacts.

There may be further vulnerabilities among suppliers that are not yet known. Based on their re-analysis of their supply chain, businesses may need to make some bold decisions to mitigate these issues. To avoid missing any weak areas, they must cover the following points in their review:

- Manufacturing suppliers' site changes, mergers, acquisitions, market volatility
- Regulatory compliance (current and future trends)
- Product lifecycle reduction, such as the obsolescence of raw materials
- Supplier constraints, such as capacity, capability, low-volume challenges and logistical risks
- Supplier solvency and financial health
- Risks due to supplier reliance on raw materials and concentration in countries likely to be impacted by climate change
- Supply chain disclosure aligned with appropriate policies, such as commitment to low carbon emissions
- Reliance on single-sourced key strategic items
- Supplier material/process changes and notification of change
- Uncertainty in and level of understanding of the supply chain, role of distributors, upstream manufacturers, complex supplier networks, complete processes and supplier maps
- Pre-screening and auditing of supplier quality:
  - Organisation quality process assets
  - Manufacturing/processing equipment
  - Potential internal process failures.

SUPPLY CHAIN MAPPING

All this data can be used to draw up a supply chain map to provide a clear overview for consistent, effective risk scoring and assessment (Box 1). This is a vital tool, both in today's post-pandemic reappraisal, and then on an ongoing and regular basis going forward. Mapping out the process will support regulatory activities, such as tracking economic operator compliance under the EU Medical Device Regulation, which makes manufacturers, importers and authorised representatives jointly and severally liable for nonconformities. For all key purchased and manufactured items, armed with the product's bill of materials, the procurement path of tier one and sub-tier suppliers can demonstrate:

- Single source relative supply chain risk score
- Material demand chain: material type, processes, distribution, sub-tier suppliers (first level)
- Supplier names, sites and geographical locations
- Dual-source alternatives and preferences for primary and secondary sourcing

BOX 1: ASSESSING SUPPLIERS

Owen Mumford assesses the following across all platforms within the supply chain using quantifiable weighted criteria:

- Quality performance of the supplier
  - Delivered product
  - Certification
  - Audit performance
  - Quality improvement
  - Supplier-related complaints and non-conformance report responses.
- Commercial aspects
  - Supplier dependency
  - Supply chain risk
  - Ability to deliver performance
  - Strategic importance
  - Frequency of orders
  - Financial health.
- Supplier features
  - Market changes
  - Quality management systems
  - Quality organised strength
  - Sub-contracting.
- Manufacturing risk
  - Criticality to process
  - Multi-code per supplier
  - Single-source or multi-site
  - Qualification lead time.
- Geographical risk
  - Natural disasters.

- Strategic and generic procurement supplier agreements, including robust, active notification of change processes and aligned safety stock policies
- Validation level information and recovery time objectives
- Commercial engagement splits for dual-sourced fully validated supply chains.

Every medical device manufacturer will discover different patterns of how risks have morphed as a result of covid-19, and must therefore carry out a deep and urgent reappraisal of their supply chain as they are likely to consistently encounter the danger of commercial damage if they fail to do so. Some of the changes we are now experiencing are likely to be permanent, and the pandemic has alerted businesses, governments and regulators alike to risks in the medtech supply chain that were previously under-recognised, or not even recognised at all. Those that begin their reappraisal soon are likely to be well prepared and more capable of weathering the storms of the future; such capability will rapidly become a significant source of competitive advantage.

"Some of the changes we are now experiencing are likely to be permanent, and the pandemic has alerted businesses, governments and regulators alike to risks in the medtech supply chain that were previously under-recognised, or not even recognised at all."

ABOUT THE AUTHOR

John Swift is Head of Supply Chain at Owen Mumford. He is an experienced operations programme manager with a successful track record working throughout the supply chain, covering procurement, supplier management, invention, development and manufacture, as well as promotion, sales and distribution. Mr Swift has experience in applying and adapting skills across both large corporations and SMEs, and has worked in multiple industries, including medical device, aerospace and defence, rail, chemical, automotive and printing.

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2. *Williams SC, "Plastics Shortage Hits Plastic Parts Supply Chain". ISM Blog, Apr 2021.*

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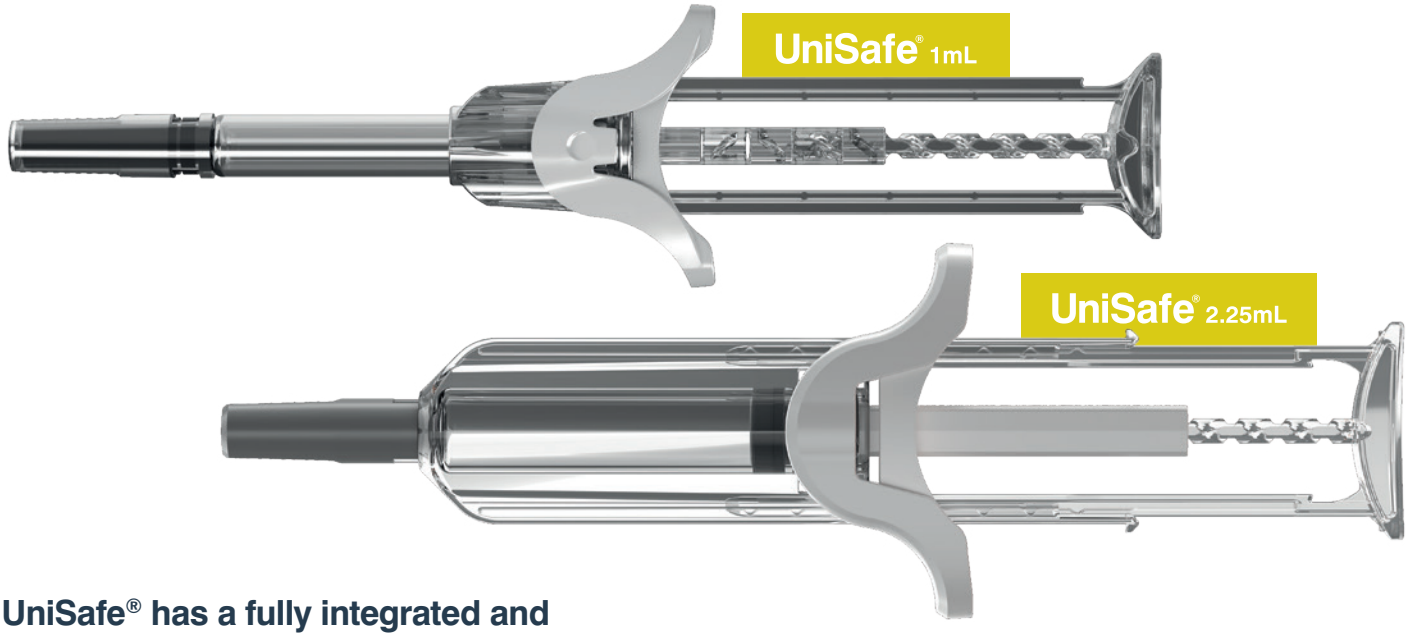

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UPDATE ON OXYCAPT™ MULTILAYER PLASTIC VIAL AND SYRINGE

In this article, Hiroki Hasegawa, Researcher, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, discuss the advantages of OXYCAPT™ multilayer plastic vial and syringe, which combine the benefits of cyclo-olefin polymer with excellent oxygen and UV barrier properties. In particular, the authors focus on recent studies that highlight OXYCAPT's very low levels of extractables.

Compared with five years ago, the use of plastic has become much more popular in the pharma industry. As a result, more and more customers have started considering plastic vials or syringes. Although glass used to be considered the best option to protect drugs from oxygen and other negative factors, some critical issues have been pointed out with it, such as delamination, pH shift and breakage. In particular, these problems are especially prevalent with protein-based drugs, such as biologics and gene and cell therapies, that are stored at low or ultra-low temperatures.

> "MGC has developed OXYCAPT™ multilayer plastic vial and syringe, which provides the myriad advantages of COP along with high oxygen and UV barrier properties."

To avoid these problems, cyclo-olefin polymer (COP) vials and syringes are sometimes used for such biologics. COP has some excellent features – including very low levels of extractables, low protein adsorption, high break resistance and excellent pH stability – but it is obvious that its oxygen and ultraviolet (UV) barrier properties are very poor. To overcome the situation, Mitsubishi Gas Chemical (MGC) has developed OXYCAPT™ multilayer plastic vial and syringe, which provides the myriad advantages of COP along with high oxygen and UV barrier properties (Figure 1).

Figure 1: The OXYCAPT™ multilayer plastic vial and syringe.

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OXYCAPT™ OVERVIEW

OXYCAPT™ consists of three layers – the inner layer in contact with the drug product and the outer layer are made of COP, while the middle oxygen barrier layer is made of MGC's novel polyester (Figure 2). Thanks to this multilayer structure, OXYCAPT™ is able to provide the following key benefits:

- Excellent oxygen barrier
- High water vapour barrier
- Excellent UV barrier
- Very low levels of extractables
- High pH stability
- Low protein adsorption and aggregation
- Silicone-oil free barrel
- High transparency
- High break resistance
- Easier disposability
- Light weight.

There are two variants of OXYCAPT™ available – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier. According to some of MGC's internal studies, OXYCAPT-A can keep a lower oxygen concentration in its headspace than Type I glass, thanks to its oxygen absorbing function. While OXYCAPT-P lacks an oxygen absorbing function, it provides an excellent oxygen barrier; the oxygen barrier of OXYCAPT-P Vial is about 20 times better than that of a COP monolayer vial (Figure 3).

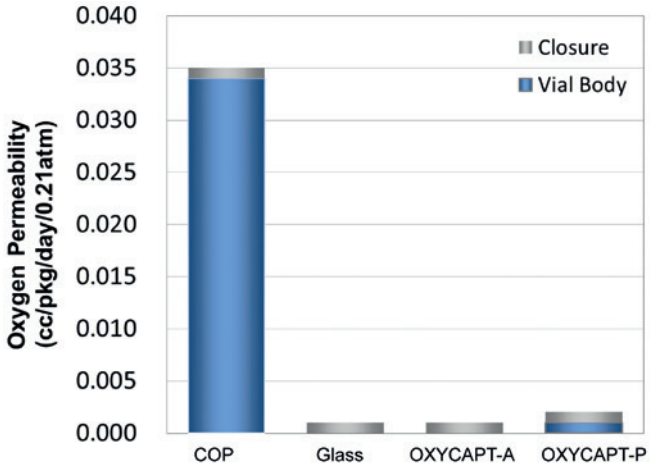


Figure 3: Comparison of the oxygen barrier properties of glass, COP, OXYCAPT-A and OXYCAPT-P.

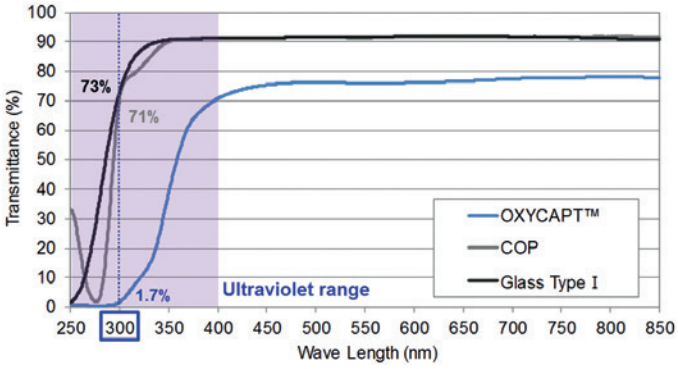


Figure 4: Comparison of the percentage of 300 nm UV light transmitted through Type I glass, COP and OXYCAPT™.

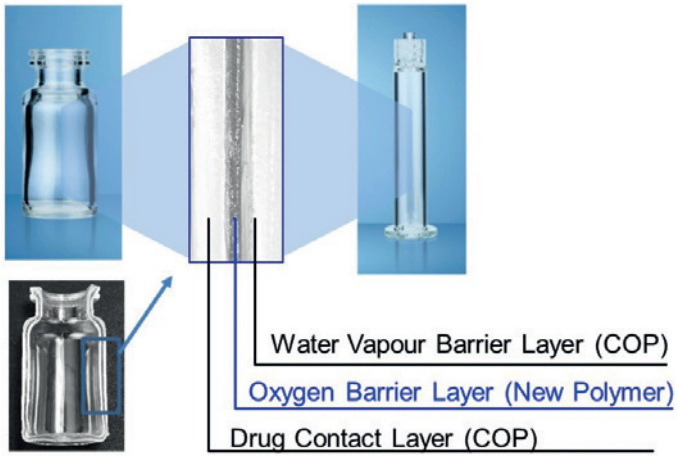


Figure 2: Multilayer structure of OXYCAPT™.

OXYCAPT™ also has excellent UV barrier properties. For example, although about 70% of 300 nm UV light transmits through glass and COP, only 1.7% of 300 nm UV light transmits through OXYCAPT™ (Figure 4). MGC has confirmed that this feature contributes to the stability of biologics.

However, when it comes to acting as a barrier to water vapour, OXYCAPT™ cannot reach the performance of glass. However, its properties in this regard are similar to those of COP, which has seen extensive use in primary containers for injectable drugs and easily meets the water vapour barrier requirements set out by ICH guidelines.

MGC conducted a pair of studies to demonstrate OXYCAPT's extremely low levels of extractables. The first study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Five solvents – distilled water, 50% ethanol, NaCl, NaOH and H3PO4 – were selected, and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, no impurities were detected in any of the OXYCAPT™ containers. The second study was conducted to confirm inorganic extractables from OXYCAPT™. The level of extractables demonstrated was similar to that typical of COP, which is well-known as an extremely pure polymer, and lower than that of Type I glass.

OXYCAPT™ vial and syringe are produced by co-injection moulding technology. Although this technology has been used in the production of beverage bottles for many years, MGC is the first company to succeed in applying it for the production of multilayer plastic syringes. MGC has also developed inspection methods for testing the oxygen barrier layer. All of the containers are 100% inspected by state-of-the-art inspection machinery.

> "The target therapeutic application of OXYCAPT™ is biologics. As ICH Q5C mentions, oxidation is one of the primary causes of protein instability. As such, the high oxygen and UV barrier properties of OXYCAPT™ contribute directly to the stability of biologics."

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: MGC's OXYCAPT™ product portfolio.

CURRENT PRODUCT OFFERING

MGC can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-standard nest and tub formats. The nest and tub are primarily sterilised using gamma radiation. There are 2, 6, 10 and 20 mL sizes for vials, and 1 mL long and 2.25 mL sizes for syringes (Table 1). MGC is happy to provide samples for initial testing free of charge.

Each polymer meets the requirements set out by United States Pharmacopeia (USP) <661>, USP <87>, USP <88> and all relevant European Pharmacopoeia (EP) regulations. Furthermore, each polymer has been filed in the US FDA's drug master file (DMF). The vials and syringes also comply with the USP and EP, and have FDA DMF numbers. Regarding the syringes, the products are produced and controlled in accordance with ISO 13485.

"The latest studies have shown an outstanding characteristic of OXYCAPT™ – extremely low levels of extractables."

The target therapeutic application of OXYCAPT™ is biologics. As ICH Q5C "Stability of Biotechnological/Biological Products" mentions, oxidation is one of the primary causes of protein instability. As such, the high oxygen and UV barrier properties of OXYCAPT™ contribute directly to the stability of biologics. Customers have also recently started evaluating OXYCAPT™ vials for their gene and cell therapies. MGC's RTU vials and syringes sterilised by gamma radiation are ideal for these protein-based drugs.

In addition, MGC believes that OXYCAPT™ is well suited to adrenaline, as it is well-known to be an oxygen-sensitive drug. Furthermore, as glass syringes suffer more from breakages than plastic ones, they are inherently less suitable for emergency drugs. As such, some suppliers are

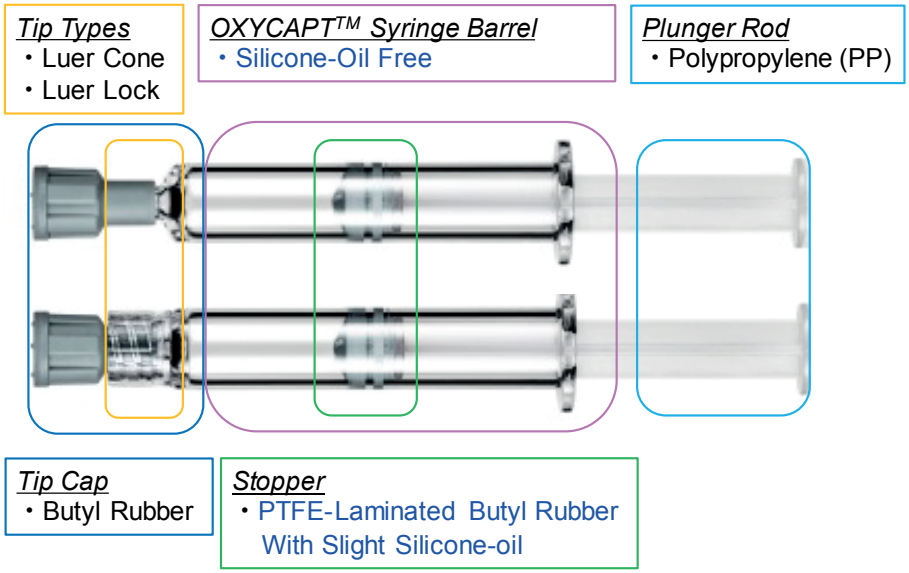


Figure 5: Components of an OXYCAPT™ syringe.

investigating plastic for the development of new pen injectors for emergency applications.

EXTRACTABLES STUDY FINDINGS

The latest studies have shown an outstanding characteristic of OXYCAPT™ – extremely low levels of extractables. An organic and elemental extractables study, which was performed in collaboration with an outsourcing pharmaceutical company, was conducted using MGC's container closure system (CCS) comprised of a 1 mL long OXYCAPT-P syringe, custom-ordered PTFE laminated butyl rubber stopper, and a normal butyl rubber tip cap (Figure 5).

Analytical method	Solution	AET (ppm)	Compounds found above AET
HS-GC-MS	0.1% PS-20	0.3	**No compound detected above AET**
	pH 3 buffer		
	pH 10 buffer		
GC-MS	0.1% PS-20	1.5	**No compound detected above AET**
	50% ethanol		
	pH 3 buffer		
	pH 10 buffer		
	50% ethanol by speed vac		
LC-UV-MS	0.1% PS-20	1.5	**No compound detected above AET**
	50% ethanol		
	pH 3 buffer		
	pH 10 buffer		
	50% ethanol by speed vac		

- AET was decided by calculation with reference of butylated hydroxytoluene (BHT) for GC-MS and LC-UV-MS or toluene for HS-GC-MS.
- As to 50% ethanol, the different sample work-up procedures were conducted to target different polarities.
- In case of '50% ethanol' in 'Solution', extraction was conducted in sample work-up to target non-polar and volatile compounds.
- In case of '50% ethanol by speed vac' in 'Solution', evaporation was conducted in sample work-up to target polar and less volatile compounds.

Table 2: Results of an organic extractables study using the OXYCAPT™ syringe CCS.

In order to detect and quantify organic analytes, volatile compounds were measured by headspace gas chromatography-mass spectrometry (HS-GC-MS). Moreover, non-polar, volatile and semi-volatile compounds were measured by GC-MS, whereas LC-UV-MS was used to detect compounds with varying polarity and volatility. Furthermore, with the OXYCAPT™ CCS, levels of the elemental impurities specified in ICH Q3D plus tungsten were detected and quantified by inductively coupled plasma mass spectrometry (ICP-MS).

These studies were conducted by a 48-hour incubation at 50°C of the OXYCAPT™ CCS with four different formulations:

- 0.1% aqueous polysorbate 20 (PS-20)
- 0.1 M phosphate buffer at pH 3
- 0.1 M phosphate buffer at pH 10
- 50% ethanol solution.

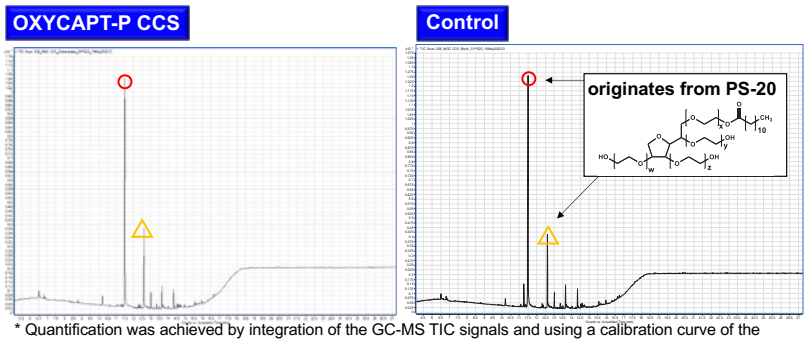
These extraction solutions cover those outlined in the latest draft of USP <665>. After incubation, a sample work-up for each solvent and analysis method was performed. Then it was confirmed whether there were any organic extractables that exceeded the analytical evaluation threshold (AET) using analytical devices. Each AET of HS-GC-MS, GC-MS and LC-UV-MS was determined by calculation with respect to the safety concern threshold (1.5 µg), filling volume of the syringe, maximum number of syringes administered per day and the concentration factor due to sample work-up. The results of analysis with HS-GC-MS, GC-MS and LC-UV-MS all showed no organic compound exceeded the AET with the OXYCAPT™ CCS (Table 2).

Figure 6 shows the GC-MS chromatogram with 0.1% aqueous PS-20. As shown in this graph, some peaks that originate from PS-20 used in the sample work-up exceeded the AET (1.5 ppm) in both the OXYCAPT™ CCS and control. However, there was no peak originating from OXYCAPT™ CCS above the AET. Furthermore, Figures 7 and 8 show the LC-UV and HS-GC-MS chromatograms for 0.1% aqueous PS-20, respectively. As is the case with GC-MS, there were no peaks originating from the OXYCAPT™ CCS detected in either analysis. Moreover, there were no peaks originating from OXYCAPT™ CCS detected with 0.1 M phosphate buffer pH 3, 0.1 M phosphate pH 10 or 50% ethanol either.

In the study with ICP-MS, no elemental impurities exceeded their permitted daily

No volatile and semi-volatile compound that originates from OXYCAPT™ CCS was detected above AET (1.5 ppm) in 0.1 % PS-20 solution.

- The chromatogram with OXCAPT™ CCS is almost same with the control.
- Signals exceeding above AET originate from PS-20 used in the sample work-up*.

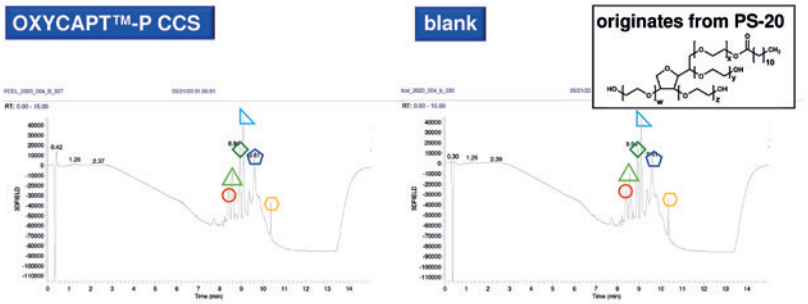


* Quantification was achieved by integration of the GC-MS TIC signals and using a calibration curve of the external reference BHT.

Figure 6: GC-MS chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

No compound with varying polarity and volatility that originates from OXYCAPT™ CCS was detected above AET (1.5 ppm) in 0.1 % aqueous PS-20.

- The chromatogram with OXCAPT™ CCS is almost same with the control.
- Signals exceeding above AET originate from PS-20 used in the sample work-up*.

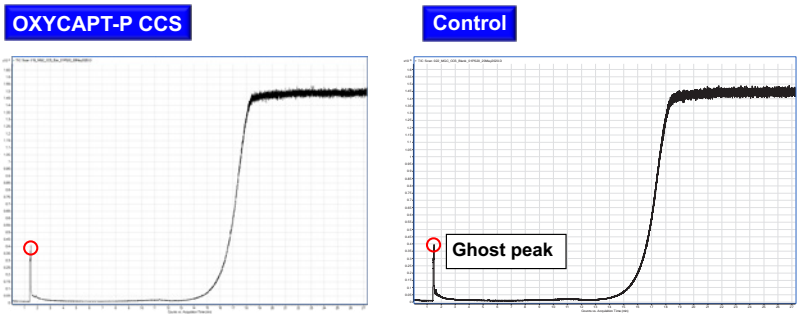


* Quantification was achieved by integration of the LU-UV signals (λ = 220 nm) and using a calibration curve of the external reference BHT.

Figure 7: LC-UV chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

No volatile compound that originates from OXYCAPT™ CCS was detected above AET (0.3 ppm) in 0.1 % aqueous PS-20.

- The chromatogram with OXCAPT™ CCS is almost same with the control.



* Quantification was achieved by integration of the HS-GC-MS TIC signals and using a calibration curve of the external toluene reference.

Figure 8: HS-GC-MS chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

exposure (PDE) as outlined in ICH Q3 (Table 3). Tungsten, which is not listed in ICH Q3D, was not present at a significant level. This result indicates that OXYCAPT™ can contribute to a safety assessment for drugs and the pH stability of drug solution.

CONCLUSION

In addition to the existing data, the latest study results showed that OXYCAPT™ CCS has an excellent resistance to aqueous surfactant, acid, alkali and alcohol solutions. As such, OXYCAPT™ CCS, along with its other well-established benefits, can contribute to the safety and efficiency of biopharmaceuticals and gene and cell therapies owing to its extremely low level of organic extractables and elemental impurities.

ABOUT THE COMPANY

Mitsubishi Gas Chemical is a major chemical products manufacturer operating across a wide range of industries. In the field of drug delivery, the company has developed OXYCAPT™ vial and syringe from a novel polymer, as an alternative to glass primary packaging.

ABOUT THE AUTHORS

Hiroki Hasegawa is a researcher in the Advanced Business Development Division at MGC. He gained a diploma in science in 2013 and a master's degree in science in 2015 from Osaka University (Japan). Since April 2015 he has been working for MGC, in charge of macromolecular science, especially in the composition development of thermosetting resin. Since 2018 he has been part of the team developing multilayer plastic vials and syringes for biologics.

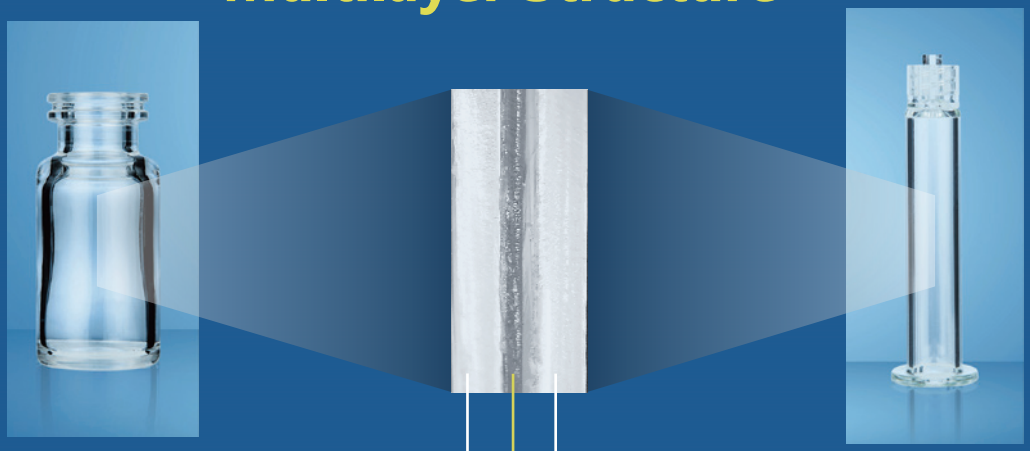
Tomohiro Suzuki joined MGC in 1998. He belonged to the Oxygen Absorbers Division until 2011, after which he was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT™ development team. Since then, he has been in charge of marketing for OXYCAPT™ vial and syringe. His current position is Associate General Manager.

Element	0.1% PS-20 solution		pH 3 buffer solution		pH 10 buffer solution		PDE (µg)
	Concentration	Amount administered with 5 syringes (µg)	Concentration	Amount administered with 5 syringes (µg)	Concentration	Amount administered with 5 syringes (µg)	
Ag	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
As	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	15
Au	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	100
Ba	< 0.1	< 0.5	0.1	0.5	0.1	0.5	700
Cd	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	2
Co	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	5
Cr	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	1100
Cu	< 0.1	< 0.5	< 0.1	< 0.5	0.1	0.5	300
Hg	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	3
Ir	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
Li	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	250
Mo	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	1500
Ni	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	20
Os	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
Pb	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	5
Pd	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Pt	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	10
Rh	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Ru	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Sb	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	90
Se	< 0.5	< 2.5	< 0.5	< 2.5	< 0.5	< 2.5	80
Sn	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	600
Ti	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	8
V	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
W	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	n.a.

Table 3: Concentration of each elemental impurity listed in ICH Q3D plus tungsten in a study with ICP-MS.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Small Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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THE FUTURE OF CONTAINER-LEVEL TRACEABILITY FOR PREFILLABLE SYRINGES

In this article, Sam Eubanks, Vice-President of Software Development, and Hervé Soukiassian, Associate Director, R&D Project Management, both of BD Medical – Pharmaceutical Systems, discuss the BD traceability solution. This concept under development aims to deliver traceability at the unique container level from manufacture to the point of care.

Pharmaceutical companies must address a triple challenge: ensuring compliance to serialisation mandates[1,2] and assessing new digital technologies to augment manufacturing efficiency and safety,[3] all while keeping an eye on tomorrow's factory-to-point-of-care (POC) traceability requirements.[3] BD proposes a way forward on all three challenges, starting with container-level traceability for fill-finish operations for prefillable syringes (PFSs).

Serialisation directives are now in place in more than 30 countries, mandating greater visibility and accountability for drug product custody along supply chains.[4] However, existing serialisation solutions limit traceability to the saleable unit level only (i.e. the secondary packaging),[1,2] leaving a door open for falsified or poor-quality medicines to make their way to the point of consumption (pharmacy retail shelves, hospitals and patients). There are also implications further upstream. Because the PFS is associated with the secondary packaging only at the end of the manufacturing line, in these cases, serialisation cannot contribute to preventing and sorting out mix-ups earlier in the fill-finish process. This represents a missed opportunity.

BD, a leading provider of drug delivery solutions, has teamed up with industry-leading partners in tagging and traceability technologies to develop a comprehensive solution that goes beyond compliance to deliver traceability at the unique container level. The goal of the programme is ultimately to ensure the integrity of the drug product at the point of consumption through a unique combination of device tagging, supply chain tracking and end-user/patient authentication.

In a first phase, the BD traceability solution will concentrate on applying the advantages of unique container-level traceability to pharma manufacturing operations. Subsequent phases will consist of expanding container-level traceability beyond pharma fill-finish operations to cover distribution and the POC.

OVERVIEW OF THE BD TRACEABILITY SOLUTION CONCEPT

With the BD traceability solution concept, ready-to-fill syringes will incorporate a unique identifier (UID) using either data matrix or radio frequency identification (RFID) technologies. At the end of the manufacturing process at BD, tagged syringes will be sealed into tubs and their UIDs will be read and aggregated to the tub/nest ID in an encrypted database. This aggregation of parent and child units will ensure tag readability prior to delivery to the customer filling line and will establish both data integrity and syringe pedigree.

When the syringes are loaded onto customer filling lines, one scan of the tub/nest ID will be enough to associate it with

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"As the product moves out of the manufacturing site and down the supply chain, a serialised pedigree of the combination drug product can be created in a secure, fully encrypted cloud-based repository."

the current batch. Each unique syringe ID will therefore be associated to the product filling batch and API code. This is meant to accomplish three goals:

- Ensure compliance to 21CRF 610.14 US FDA General Biological Products Standards[5]
- Establish a permanent link between syringe and API
- Enable the segregation of batches.

At each subsequent process step, the syringe ID can be cross-checked to prevent mix-ups. The process is not expected to impact the overall equipment efficiency of the production line. Industry-leading hardware and software solutions will provide the capabilities to access syringe container ID and ensure ease of integration at the customer site.

A cloud-based data exchange and management system will ensure linkages between the unique container ID and the serialised drug product. As the product moves out of the manufacturing site and down the supply chain, a serialised pedigree of the combination drug product can be created in a secure, fully encrypted cloud-based repository.

At the end of the process, when the patient or caregiver is ready to administer the medication, a final query can be made to confirm the drug's clean pedigree and authenticity, based on its unique movement through the pharmaceutical supply chain.

BUILDING VALUE BEYOND COMPLIANCE

The BD traceability solution is expected to enable precise, unit-level visibility with the potential to log the container's passage through each manufacturing step. This data – which can include the individual container's manufacturing information – will endow production managers with unique tools to help in process improvement as well as preventing and resolving issues accurately and efficiently.

The BD traceability solution is designed to provide a verifiable pedigree from manufacture to the POC. This pedigree will be based on a chain of custody record building upon the immutable core of the container's UID.

A TURNKEY SOLUTION FOR TRACEABILITY DURING THE FILL-FINISH PROCESS

The BD traceability solution is expected to address the following customer needs:

Mix-Up Prevention

Mix-ups carry a hefty price tag in terms of staff time and lost product.[6] For example, a syringe might be filled with a different drug from the one mentioned on the label. Colour-coded label rings are limited to their ability to distinguish multiple drug products, and they cannot distinguish batches, especially if the mix-up occurs before the labelling step. BD pretagged syringes carrying serial numbers should help to prevent mix-ups and resolve queries prior to, during and after the manufacturing process.

Enable Batch Segregation

The BD traceability solution is expected to provide manufacturers with unit-level visibility of key manufacturing processes by giving production line managers precise data on the position and time of each unit at each stage of the production process. This should enable rejected units to be traced back precisely to each discrete step of the fill-finish operation. Such accuracy is meant to help limit batch segregation to affected units only, which, in turn, could reduce the costly tendency to over-segregate or dispose of an entire batch due to limited process visibility. By optimising investigations and batch segregation, the solution is expected to help maintain the continuity of production.

"The BD traceability solution is expected to provide manufacturers with unit-level visibility of key manufacturing processes by giving production line managers precise data on the position and time of each unit at each stage of the production process."

Speeding Reconciliation and Line Clearance

The BD traceability solution is meant to provide unit-by-unit accountability for every container on the filling line, the batch it belongs to, its status (i.e. successfully filled, rejected, etc) and potentially other information, thus automating reconciliation and accelerating line clearance. It will help ensure that no container is left behind when a new batch starts up.

Faster Quality Assurance Investigations

The BD traceability solution is meant to accelerate quality assurance (QA) investigations when process deviations or other issues arise during the fill-finish process. Having syringe traceability data to hand would enable investigators to link issues to the specific containers and batches concerned. As more than one batch of syringes may be used to produce a single batch of a finished product, the BD traceability solution should help investigators limit the number of finished product batches requiring investigation – which should significantly limit the number of batches affected in the case of an expanded-scope investigation.

Effective, Targeted Action in the Case of Recalls

Product recalls, whether they concern a medication or a medical device, typically require casting a wide net to ensure that a potentially harmful product has been fully eliminated from the market. The BD traceability solution is expected to provide QA/quality control teams with a high degree of precision in identifying the units or batches to be recalled. This is expected to help companies work rapidly and proactively to locate recalled units and issue product withdrawal orders to appropriate parties, preventing the products progressing further down the supply chain.

Compliance

The BD traceability solution incorporates industry best practices as defined by GS1.[7]

"The BD traceability programme is focused on delivering reliable execution and end-to-end, cost-effective implementation of device, hardware and software development, installation, on-site validation and maintenance."

BD TRACEABILITY SOLUTION EXPECTED TO HELP DE-RISK YOUR TRACEABILITY INVESTMENT

With hundreds of pharmaceutical and biotechnology companies placing their confidence in its products, BD is a natural partner for the provision of serialised syringes.[8] The company offers an open platform solution, aimed at meeting customer requirements for RFID or data matrix technologies and the accompanying software. The BD traceability programme is focused on delivering reliable execution and end-to-end, cost-effective implementation of device, hardware and software development, installation, on-site validation and maintenance.

By choosing the BD traceability solution and the automatic identification and data capture technologies and standards they incorporate,[7] pharmaceutical companies will ensure that compatibility and interoperability will be maintained even as technologies evolve. As a container supplier, BD is well positioned to support new data use cases with manufacturing data related to container UID.

The BD traceability solution draws on the expertise of the BD Software Technology Solutions (STS) team, comprised of 1,500 software engineers that partner with BD business units to design, develop and commercialise integrated solutions. STS provides software solution delivery, technology platform harmonisation and solution development services.

GOING FORWARD

BD would like to help pharma customers transition their manufacturing lines to unit-level traceability with a coherent path towards end-to-end traceability. BD is working to provide a comprehensive solution that provides proven, industry-leading technologies along with the industry know-how and support of a world leader in PFS technology.

BD proposes to partner with customers interested in this comprehensive traceability solution. This will allow interested customers to specify the use-case requirements to be built into the solution, and test the tagged syringes, production line hardware and software in a pilot project.

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers PFSs, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

ABOUT THE AUTHORS

Sam Eubanks is a Vice-President of Software Development at BD, responsible for the design, development and lifecycle management activities for enterprise software solutions. He has over 23 years of experience in the software industry across various vertical markets, the last 18 of which have been within the healthcare industry. Mr Eubanks joined BD in 2015 and has led the delivery of cloud-based, deployed and mobile-enabled enterprise solutions for multiple business units. He has also led innovation and delivery for multiple enterprise software platforms, which support informatics solutions in the areas of interoperability, mobility and remote support and service. Prior to joining BD, Mr Eubanks worked at CareFusion, and at multiple software start-up companies and consulting organisations, including PricewaterhouseCoopers. He holds a BSc in Civil Engineering and an MBA.

Hervé Soukiassian joined BD Medical – Pharmaceutical Systems in 2007 and is currently managing product development of PFSs for the chronic segment, within R&D. Under his leadership, BD Neopak™ XSi™ and the BD Neopak XtraFlow™ platforms have been successfully developed and brought to market. He also contributes actively to industry initiatives such as the PDA task force and has co-authored several recently published technical papers. Prior to joining BD, Mr Soukiassian was at Hewlett Packard for 13 years in positions of increasing responsibility, developing expertise in the fields of process engineering and product development. He was also a member of the board of directors of ActiCM, a start-up company specialising in optical co-ordinate measurement machines. Mr Soukiassian graduated from the Institut National des Sciences Appliquées in Lyon (France) as a mechanical and industrial engineer, with an MA in Material.

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THE FOURTH INDUSTRIAL REVOLUTION – ROBOTICS AND THE LABORATORY

In this article, Marc Brown, PhD, Co-Founder and Chair of Scientific Committee, and Jon Lenn, PhD, Chief Scientific Officer, both at MedPharm, look at the company's implementation of automated robotic systems in enhancing workflow and the company's plans for the future implementation of robotics in formulation development.

Industry has been rapidly advancing since the 18th century with distinct periods of growth, or "revolutions", sparked by major innovations. The introduction of steam and electricity were the first two waves of the industrial revolution that radically changed the manufacturing economy on a global scale. The ability to harness power led to the rapid growth of technological innovations to automate previously manual tasks, resulting in more efficient production. The third industrial revolution was realised with the invention of computers, electronics and data storage. We are now in the middle of a fourth industrial revolution that seeks to combine physical and cyber technological advances. But how does this apply to life sciences and laboratory services, such as those offered by MedPharm?

> "Many laboratory tasks lend themselves to automation, thereby freeing experienced scientists to think critically, process data and provide complex interpretation, contextualisation and risk mitigation strategies for clients."

AUTOMATING SAMPLE PREPARATION

Any well-controlled experiment has the capacity to generate a large number of samples, and the sample volume can grow exponentially when laboratory experiments can run on a continuous cycle. Many laboratory tasks lend themselves to automation, thereby freeing experienced scientists to think critically, process data and provide complex interpretation, contextualisation and risk mitigation strategies for clients.

MedPharm's approach to integrating this fourth revolution was to critically evaluate the experimental workflow from end-to-end. Many experimental assays have been redesigned using a higher throughput approach. Simply switching sample collection to standard microplates allows for integration between microplates, instrumentation and equipment from different suppliers. MedPharm uses liquid-handling robots for routine sample preparation, which are further coupled with sample managers attached to analytical instrumentation. This allows samples to be processed and analysed 24 hours a day in parallel to other experiments. This automated workflow has been implemented in MedPharm's analytical, preformulation performance testing and tissue culture departments. This higher throughput approach has decreased timelines, cut down on experimental variation, tightened precision and decreased inaccuracies.

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"Many commercially available systems do not consider sample collection standards, thereby limiting the integration into other instrumentation. MedPharm's approach was to develop and engineer its own systems based on the company's 25 years of experience with the older platforms."

AUTOMATION OF IVPT, IVRT, PREFORMULATION AND PROCESS DEVELOPMENT

In vitro release testing (IVRT) and *in vitro* permeation testing (IVPT) are two critical tests and the gold standard for the development of any topical or transdermal product. The systems or diffusion cells used in these experiments were developed decades ago – well before higher throughput experimental design was conceived. The original systems are highly manual, requiring scientists to spend a large amount of time to set up, collect and process the samples. Many commercially available systems do not consider sample collection standards, thereby limiting the integration into other instrumentation. MedPharm's approach was to develop and engineer its own systems based on the company's 25 years of experience with the older platforms. Some of the key concepts that were built into these designs were automation of the experiment, sample collection in microplates, optimised fluidics for human tissue (e.g. IVPT) and synthetic membranes (e.g. IVRT), and computer-controlled data collection.

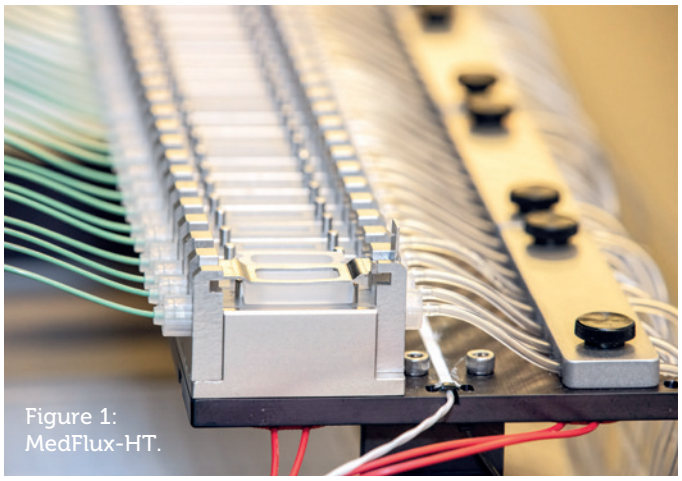

Figure 1: MedFlux-HT.

MedPharm's automated flow-through diffusion cells (MedFlux-HT®) are used routinely for IVPT experiments for R&D and regulated studies (Figure 1). This system has an integrated transepidermal water loss (TEWL) instrument that measures 32 diffusion cells simultaneously to ensure that the tissue maintains its barrier integrity. The TEWL instrument has an adapter that can be attached to Transwell permeable supports (Corning, NY, US) for experiments that use reconstructed tissue (e.g. skin, mucosal membranes, respiratory and eye).

MedPharm's automated vertical diffusion cell system (MedStat-HT®) is routinely used for IVRT where synthetic membranes are used in experiments to optimise thermodynamics, compare product sameness and as a quality control during product development (Figure 2). One example of design improvement is sample collection using highly precise and reproducible peristaltic pumps that self-eliminate air bubbles (a common problem in manual systems). This system also integrates computer-controlled sample collection and simultaneous receptor solution collection into microplates.

Figure 2: MedStat.

MedPharm has also implemented automated robotic systems such as the KingFisher™ Flex Purification System (Thermo Fisher Scientific, MA, US) in its tissue culture labs. This fully automated system yields high-speed purification of nucleic acids, proteins and cells using a similar microplate approach and has generated excellent reproducibility and quality.

Additionally, MedPharm has incorporated automation into preformulation and process development workflows. MedPharm's use of liquid handlers and robots to automate steps in preformulation allows drug solubility and stability to be assessed more accurately within various solvents and solvent systems, reducing the risk in variability when compared with human sampling. When assessing longer-term physical stability, automated instrumentation, such as a LUMiSizer® (LUM, Berlin, Germany), provides a more accurate prediction when compared with the harsher centrifugation technique, where marketed products are often observed to phase separate. Within process development and scale-up, MedPharm uses IKA Lab (Oxford, UK) reactors for identification and optimisation of critical processing parameters and the reproducible manufacturing of larger batches in future development.

"MedPharm has incorporated automation into preformulation and process development workflows. MedPharm's use of liquid handlers and robots to automate steps in preformulation allows drug solubility and stability to be assessed more accurately within various solvents and solvent systems, reducing the risk in variability when compared with human sampling."

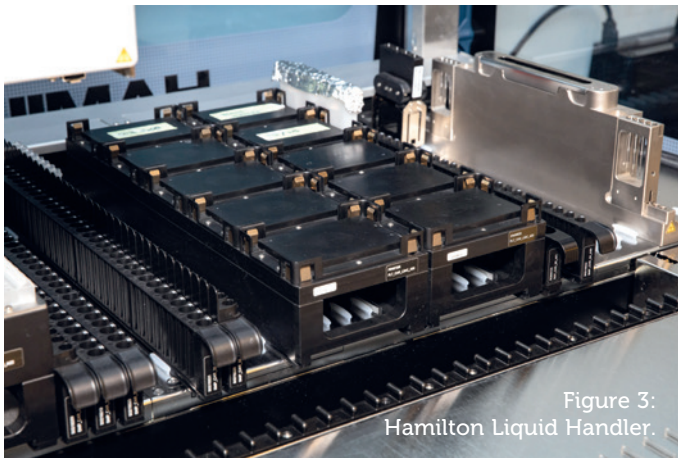

Figure 3: Hamilton Liquid Handler.

THE FUTURE

The next steps for MedPharm will be to implement robotics in formulation development. These robotics have similarities to liquid-handling robots, such as the Hamilton Liquid Handler (Figure 3), but are specifically designed to handle a range of excipients with complex viscosities used in the development of semi-solid formulations. These platforms integrate low powder weighing capability (low milligrams) to allow compound sparing when clients have a limited amount of active substance but will also allow for a much larger design of experiments to increase excipient testing.

MedPharm has over 25 years of experience in developing topical and transdermal products – meaning it has performed millions of experiments with the outcomes interpreted by the company's expert scientists. The next step is to develop structured databases or "large data" that can be mined for experimental trends relating to physiochemical properties, excipient compatibility, chemical solubility and stability, product performance, biological delivery and activity. This data could ultimately be used in machine learning (e.g. artificial neural networks) to identify trends that can be used in predictive experimental designs.

ABOUT THE COMPANY

MedPharm is a leading global contract provider of topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development timelines for proprietary pharmaceutical and generic customers through their unique, cost-effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations. MedPharm is recognised for its scientific rigor by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK, with over 20 years of experience developing topical products.

ABOUT THE AUTHORS

Professor Marc Brown, PhD, is the Chair of Scientific Committee, co-founded MedPharm in August 1999 and has been the guiding force behind MedPharm's scientific developments and intellectual property. He has held the position of Professor of Pharmaceutics in the School of Pharmacy, University of Hertfordshire (UK) since 2006 and retains visiting/honorary professorships at the Universities of Reading (UK) and King's College London (UK). He has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of over 55 products that are now on the market in Europe, America and Japan. Prior to MedPharm, he was an academic in the Pharmacy Department at King's College London.

Dr Jon Lenn, Chief Scientific Officer, has direct responsibility for MedPharm's operations in the US based out of its facility in Durham, NC. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience in developing dermatological projects with Connetics, Stiefel and GSK and has been directly involved with the development and approval of eight products. He received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

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ENHANCED PROCESS CONTROL FOR LIPID-BASED NANOPARTICLES: LNPS AND LIPOSOMES

In this article, Antonio Costa, PhD, Chief Executive Officer of DIANT Pharma, discusses the use of lipid nanoparticles in the modern drug delivery industry and introduces the DIANT system for the continuous processing of nanoparticles with integrated process analytical technology, which can provide the quality required for these injectable, complex formulations.

INTRODUCTION

Nanoparticles are once again in the spotlight, this time as a critical tool to combat the spread of covid-19. In particular, messenger ribonucleic acid (mRNA) encapsulated in lipid nanoparticles (LNPs) has been successfully manufactured, distributed and administered to populations worldwide. The high efficacy and strong protection of covid-19 mRNA-LNP vaccines has generated significant interest in them as a candidate for future vaccines and therapeutics. However, information released by the European Medicines Agency (EMA) covid-19 data leak emphasises the need to better understand quality issues observed in the LNP manufacturing process – for example, quality issues may be traced to RNA instability and LNP particle size.

mRNA-LNPS

The components of mRNA-LNPs can be divided into four main groups:

1. An ionisable, cationic lipid
2. One or more neutral/structural lipids
3. mRNA
4. Buffering systems and water.

All of these components come together to form a sophisticated and tunable delivery system. In this case, the delivery cargo is mRNA and the target delivery location is a specific tissue or cell type. There is a truly remarkable relationship between all of these components that have made LNPs a success story. To start, the mRNA, which has a particular sequence of nucleotides, is processed by ribosomes to synthesise a protein, such as a spike protein.

The ionisable, cationic lipid has multiple roles, such as promoting the encapsulation of mRNA during the LNP synthesis process and releasing the mRNA within the cytoplasm. The neutral/structure lipids, such as distearoylphosphatidylcholine (DSPC) and cholesterol, provide the general framework or structure of the particles, whereas pegylated lipids coat the surface of the LNPs and provide physical stability and enable longer circulation times in the host.

Buffering systems are important for properly forming and neutralising the particles. Additionally, water, a sometimes-overlooked component, is very important in the core structure of the LNP, providing a continuum of hydrogen bonds between the mRNA and the hydrophilic portions of the lipid components. Accordingly, the LNP formulation is a critical factor linked directly to RNA encapsulation and multiple aspects of the delivery system's overall pharmacokinetics and pharmacodynamics, including the localised target tissue or cellular expression.

LIPOSOMES

Liposomal nanoparticles have been approved as drug products throughout the world for a variety of clinical indications,

> "Liposomal nanoparticles have been approved as drug products throughout the world for a variety of clinical indications, including cancer and fungal treatments, with the highest percentage of liposomal drug products being anti-cancer therapies."

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"Although these therapeutics are very beneficial to patients, scalable processing and manufacturing technology platforms are still being developed."

including cancer and fungal treatments, with the highest percentage of liposomal drug products being anti-cancer therapies. The APIs in these drug products are typically small molecules such as doxorubicin, daunorubicin, cytarabine or irinotecan.

The basic principle of how liposomes are effective is that they deliver a high payload directly to the site of action, such as a tumour, resulting in a more efficacious and safer drug product. In brief, liposomes consist of a lipid bilayer that surrounds an aqueous compartment. The majority of liposomes that have been approved by regulatory agencies have lipid compositions that include phosphatidylcholine lipids, cholesterol and either a PEGylated or charged lipid.

The composition of the lipid bilayer plays a major role in the liposome's stability, both in storage and *in vivo* conditions, meaning that the type of lipids and their molar ratios are considered critical material attributes. For example, cholesterol is known to affect bilayer rigidity and PEGylated lipids promote steric stabilisation of the bilayer. The API can either go into the lipid bilayer or be encapsulated in the aqueous compartment. Moreover, targeting moieties can be added to the lipid bilayer to provide a direct targeting mechanism *in vivo*.

A major benefit of liposomal drug products is that they greatly reduce the side effects that occur with non-liposomal chemotherapy treatments. In addition, liposomes promote longer blood circulation times, resulting in a longer half-life of the API. Although these therapeutics are very beneficial to patients, scalable processing and manufacturing technology platforms are still being developed.

CURRENT MANUFACTURING METHODS

Current manufacturing methods to produce lipid-based nanoparticles include solvent injection, homogenisation and microfluidic mixing. Solvent injection methods are typically performed by pre-mixing ethanol with a lipid and then injecting the mixture into an aqueous phase. Solvent injection methods comprise crossflow injection, static-mixers, microfluidic mixing and turbulent jet technologies, with the latter providing a highly controllable mixing strategy. Microfluidics offer a variety of mixing techniques and various geometries have been developed to mix the solvent stream with the aqueous stream.

Each of these strategies rely on different degrees of convective and diffusive forces for mixing. For example, microfluidics may mix in a very low Reynolds number state (laminar flow), whereas crossflow injection, t-mixers and turbulent jets operate at much higher Reynolds number states (turbulent flow).

Figure 1: DIANT LF system for nanoparticle synthesis, part of the DIANT production series.

CONTINUOUS PROCESSING OF NANOPARTICLES

DIANT Pharma has introduced a series of systems that use a continuous manufacturing technology and implement a turbulent jet in co-flow. Integrated process analytical technology (PAT) provides enhanced control from particle formation throughout downstream processing, which includes ultrafiltration/diafiltration (UF/DF), purification and bioburden reduction. The DIANT system is a scalable, turnkey solution that uses only a single jet, producing particles from 0.2 LPM up to 100 LPM (Figure 1).

"The DIANT system is a scalable, turnkey solution that uses only a single jet, producing particles from 0.2 LPM up to 100 LPM."

The scalability of this technology is an important consideration when selecting processing equipment, from lab to commercial scale. The DIANT system has multiple modules and is offered as a continuous, closed system. The add-on modules include a buffer exchanger/concentration module, an active loading/surface modification module and a final purification stage/bioburden reduction module. The system can be a hybrid system, running in single unit operation or batch mode, or as an integrated system in an end-to-end continuous manufacturing process.

SR-DLS for Automatic Particle Size Control

One of the PAT tools integrated in the DIANT systems is the NanoFlowSizer

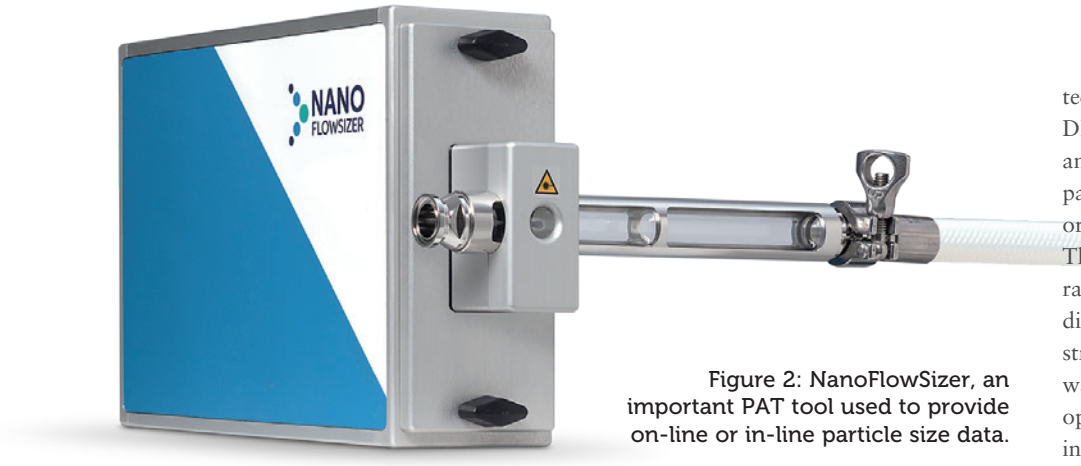

Figure 2: NanoFlowSizer, an important PAT tool used to provide on-line or in-line particle size data.

(Figure 2), a spatially resolved dynamic light scattering (DLS) technology developed by InProcess-LSP (Oss, Netherlands). This PAT tool is highly useful for measuring multiple attributes of the particles being processed, such as the Z-average (d.nm) particle size, polydispersity index (PDI), turbidity and particle size distribution (PSD). Attributes such as the Z-average, PDI and PSD are typically listed in product specifications and may be considered critical quality attributes for liposomes and LNPs.

> "By using the NanoFlowSizer and DIANT system's feedback algorithms, a highly reproducible and consistent particle size can be achieved from the beginning to the end of the processing run."

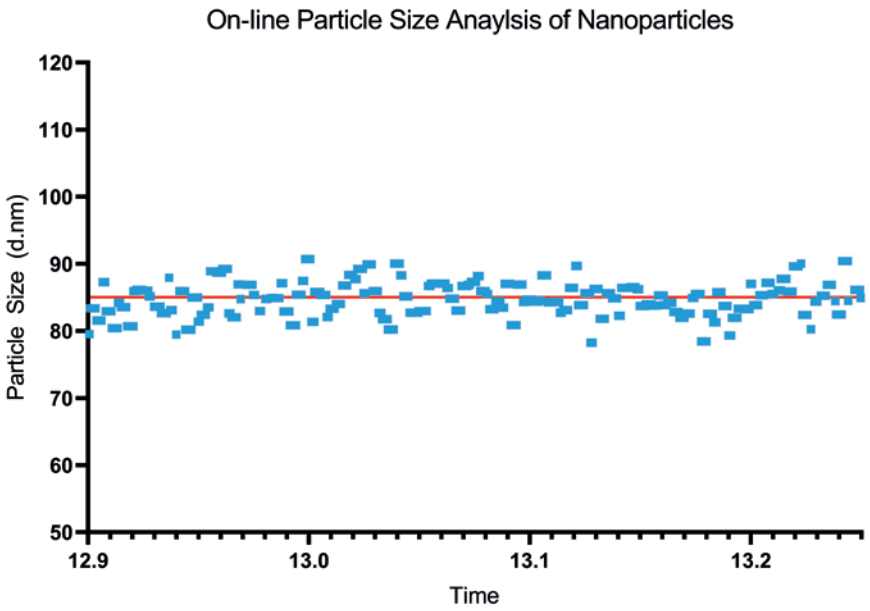

Figure 3: Example particle size data for a 30-minute run.

Spatially Resolved DLS (SR-DLS) technology was incorporated over other DLS techniques as it enables particle size analysis at high flow rates, such that the particle size can be analysed on-line and/or in-line, as opposed to at-line or off-line. The on-line/in-line approach supports a rapid assessment of the particle size and directly measures the particles in the process stream without the nanoparticles going to waste or requiring sample handling by an operator. There is also the major benefit in that the NanoFlowSizer flow cells can be cleaned or steamed in place.

Enhanced Control Using the DIANT System

By measuring the particle size on-line or in-line, the particle size measurements can be used as a feedback mechanism to control the formation of the nanoparticles. When considering that nanoparticle formation is highly susceptible to process condition changes, the added layer of protection using a feedback mechanism offers much-needed quality control. Running the system for extended durations with inevitable subtle changes occurring in the local environment can impact the overall process on the nano-level. By using the NanoFlowSizer and the DIANT system's feedback algorithms, a highly reproducible and consistent particle size can be achieved from the beginning to the end of the processing run (Figure 3).

Research and Development System – A Low Flow Starting Point

The DIANT LARU is a lower flow continuous processing system using the same jet technology found in the DIANT production series (Figure 4). This system is designed to have a low dead volume to reduce material costs, such as when working with costly lipids or mRNA. The DIANT LARU is offered with multiple add-ons, such as an in-line particle size module and a tangential flow filtration module.

CONCLUSION

LNPs have a bright future in both the vaccine and therapeutic space. However, to make the most of their potential a scalable, high-throughput processing technology is required to move smoothly from lab to commercial scale. The DIANT system, integrated with NanoFlowSizer, provides the enhanced control required to consistently produce uniform and high-quality nanoparticles.

ABOUT THE COMPANY

DIANT Pharma was founded in 2019. The company's proprietary continuous manufacturing technology for nanoparticles has a wide array of applications throughout multiple industries. The DIANT series systems use state-of-the-art nanoparticle processing technology, including a scalable jet that makes nanoparticle generation simple from R&D to production. DIANT Pharma is always looking for partners to broaden the use of their technology.

Figure 4: DIANT LARU, a research and development system for nanoparticle synthesis, scalable to the DIANT production series.

ABOUT THE AUTHOR

Antonio Costa, PhD, is the Chief Executive Officer of DIANT Pharma and has been involved with continuous processing of lipid and polymer nanoparticle formulations for over seven years. With his multidisciplinary background, he has been a key figure in the design and development of the continuous processing technology at the University of Connecticut (Storrs, CT, US). Dr Costa is the named inventor on two patents and multiple patent applications and the author of several peer-reviewed publications.

AUTOMATED LIPID NANOPARTICLE PRODUCTION: FROM PROTOCOL DEVELOPMENT TO GMP MANUFACTURE

In this article, Richard Gray, MA (Cantab), Commercial Director at Blacktrace, and Julia Rashba-Step, PhD, Vice-President of R&D and Alliance Management at Phosphorex, discuss the benefits of automated lipid nanoparticle production.

Interest in nanotechnology, including both polymeric and lipidic nanoparticles, has grown significantly in the last decade. The tremendous success of mRNA-lipid nanoparticle (LNP)-based vaccines during the covid-19 pandemic has led to further explosive growth in development and created new opportunities in this area. The unprecedented speed of development of the covid-19 LNP-based vaccines was, to a large extent, built on groundwork performed over the last 10–15 years in LNP platform development.

Nanoparticles are excellent delivery vehicles for various modalities, including nucleic acids such as mRNA, saRNA and siRNA, proteins and small molecules, as well as non-pharmaceutical products in the food, cosmetics and other industries. The function of the nanoparticle is to deliver the cargo to the action site and to protect the cargo – often referred to as an API – from degradation within the body and during storage.

Lipidic particles, including liposome and lipid nanoparticles, are spherical vesicles of various sizes (typically ranging from 30 to several hundred nanometres) and architecture, formed via self-assembly. These lipidic structures have the capacity to encapsulate both hydrophobic and hydrophilic compounds, and offer increased bioavailability and targeted delivery. To enhance the desired properties, it is feasible to functionalise the particle surface with targeting moieties such as monoclonal antibodies or their fragments. At present, most of the effort in vaccine and API delivery is focused on LNPs. However, nanoparticles formed from biodegradable polymers such as polylactic-co-glycolic acid (PLGA) also offer an excellent alternative approach to achieving controlled release.

> "Current nanoparticle production methods tend to either be batch based or use relatively large-scale, continuous flow equipment, such as membranes. Both methods have significant drawbacks."

PRODUCTION CHALLENGES

Current nanoparticle production methods tend to either be batch based or use relatively large-scale, continuous flow equipment, such as membranes. Both methods have significant drawbacks; the particle size is not very consistent and the encapsulation efficiency – the amount of drug or other cargo that ends up in the particle – can be poor, resulting in the waste of expensive materials. The minimum sample size is also typically large, causing significant problems in early-stage work where the high cost and limited availability of specialised lipids and the API restrict the amount of material available.

Many experiments need to be performed to optimise the formulation, so it is important to use as little material as possible during investigative studies and process optimisation. Furthermore, batch-based methods often require revalidation as the batch scale increases, as there are significant changes to mass transfer and other characteristics as vessels become larger. Microfluidics is an excellent solution to these problems, allowing experimental work with small quantities of materials, and offering exceptional particle size monodispersity and encapsulation efficiency, and the ability to scale up to high throughput with no change to the fundamental particle formation method.

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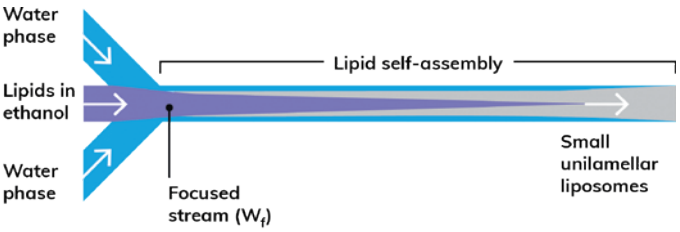

TFR = total flow rate

$$FRR = \frac{\text{water phase flow rate}}{\text{ethanol flow rate}}$$

Figure 1: Microfluidic production of nanoparticles.

> "In microfluidic systems, nanoparticles are generated at the interface of two flows, frequently a lipid – which forms the particle – dissolved in an organic solvent (such as ethanol) and a hydrophilic cargo or drug dissolved in water or an aqueous buffer."

MICROFLUIDIC GENERATION OF NANOPARTICLES

In microfluidic systems, nanoparticles are generated at the interface of two flows, frequently a lipid – which forms the particle – dissolved in an organic solvent (such as ethanol) and a hydrophilic cargo or drug dissolved in water or an aqueous buffer. When these immiscible streams meet, the lipid precipitates, then self-assembles into spherical particles encapsulating the drug (Figure 1). The resulting nanoparticle size is typically a function of LNP composition and flow rate ratio (FRR), while the polydispersity index (PDI) and encapsulation efficiency can be optimised by careful choice of flow conditions and lipid/stabiliser selection. However, like batch methods, first-generation microfluidic tools are best suited to processing a single set of reagents, making it hard to vary production protocols quickly and automatically to generate test samples from a range of lipids, polymers and APIs.

A DEMAND FOR AUTOMATION

Clearly, there is an urgent need for automated production of LNP libraries for screening and optimisation, and subsequent scale-up for cGMP production. Automation would streamline screening of nanoparticles to allow the selection of candidates with the most promising biological performance. It would also enable rapid optimisation of particle size, consistency and encapsulation efficiency – reducing cost and increasing throughput. Equally importantly, it would also enable the scale-up of the development protocol to larger-scale manufacturing without redefining and reoptimising the process.

Typical performance requirements for automated LNP production include the ability to generate a wide range of particle sizes and to modify a variety of parameters quickly and easily – for example, to evaluate different flow rates or temperatures. Pharmaceutical companies often automatically produce a plethora of drug analogues, which are then screened using automated biological assays to determine which candidates to take forward. An automated LNP system would allow rapid screening of candidate formulations against a wide range of biological targets. It is, of course, vital that any automated nanoparticle generation system integrates seamlessly with the laboratory information management system to allow validated data capture and processing, and integration with upstream and downstream processes.

A NOVEL PRODUCTION PLATFORM

The need to overcome the challenges of protocol development and enable subsequent scale-up to GMP manufacturing led one company specialising in the field of microfluidics to develop a dedicated nanoparticle production platform offering automated set-up and execution of a sequence of samples. Lipid and cargo are loaded into software-controlled reagent injection loops for serial injection of samples – the sole manual step in the protocol. A series of experiments is then executed, with pump operation, loop switching and washing performed automatically. The resulting nanoparticle samples are collected using an automated liquid handler. Particles ranging in size from 20 to 800 nm can be readily and repeatably generated, with an excellent PDI and encapsulation efficiency, for cost-effective use of expensive APIs for process development.

It is important that the LNP size and PDI are consistent from run to run. The use of 5 mL sample loops and ~250 µL samples allows multiple parameters to be explored in a single run, with automated washing of all wetted parts between samples to eliminate cross-contamination. Particle size has been shown to be consistent over FRRs ranging from 0.5:1 to 3.5:1, while being relatively insensitive to the total flow rate (TFR) (Figure 2).

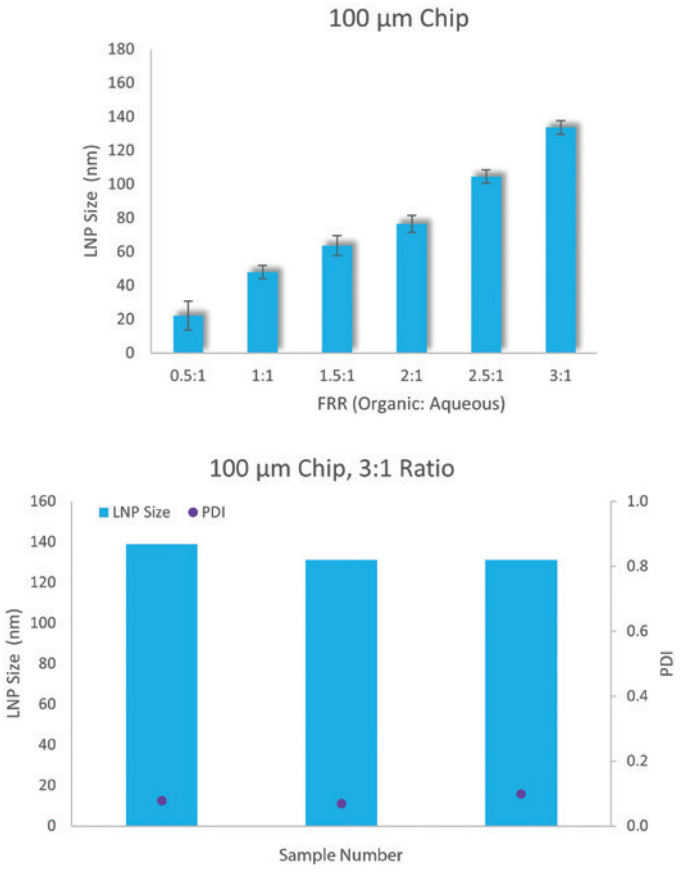

Figure 2: Particle size is consistent over a range of FRRs and relatively insensitive to the TFR for a given FRR.

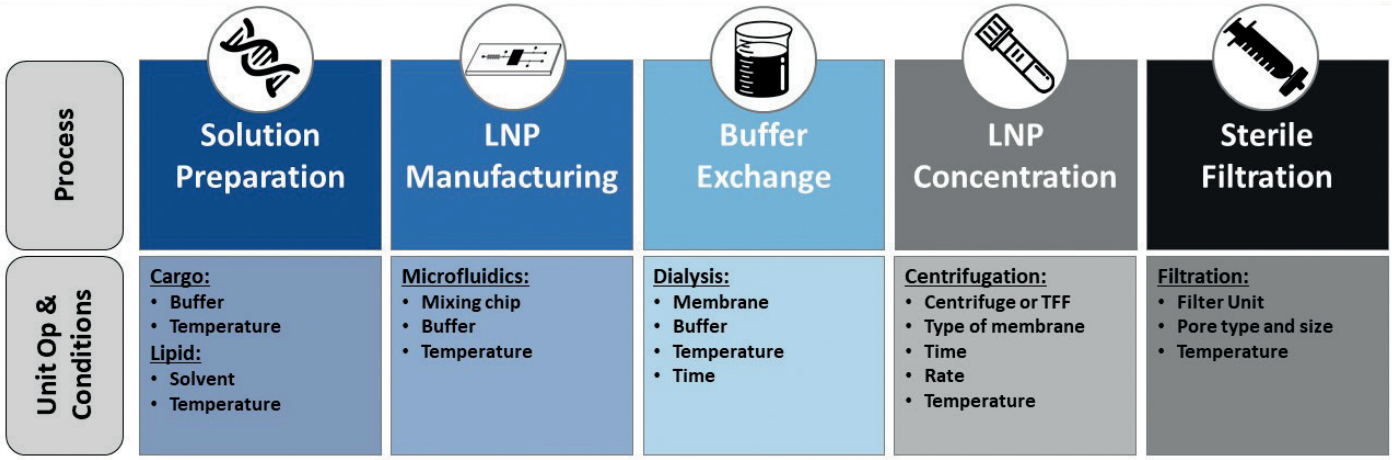

Figure 3: Key stages of LNP product and process development.

Once the desired particle size is achieved, other parameters – such as PDI, stability and charge – may be improved by using different lipids, or combinations of lipids and/or stabilisers such as cholesterol, for improved nanoparticle stability. Solubility and viscosity affect the formation rate, and processes can be optimised with different reagents by careful selection of an appropriate microfluidic chip. Chips are available that work at a low TFR for efficient use of costly reagents and APIs, while others allow operation at a very high TFR for high-throughput particle generation. Production rates for the protocol development system range from 100 µL/min to 16 mL/min per channel, allowing work with small amounts of material in early stages and later production of trials samples at higher throughput. Small amounts of sample – from 200 µL to 5 mL – can be generated during the development phase then, once the protocol is established, the process can be scaled up by operating the same system in continuous production mode for larger-scale manufacture of up to 1 L/h, without the need for revalidation. This offers the benefit of fast and economical operation, with a single system able to perform all the necessary tasks.

LNP PRODUCT AND PROCESS DEVELOPMENT

Start With the End in Mind

This newly developed automated nanoparticle system is now the focus of a collaboration with a leading contract development and manufacturing organisation (CDMO), with the goal of establishing a robust platform for LNP and polymeric particles to support nanoparticle product development, validation, scale-up and subsequent GMP production. This collaboration will provide the foundation needed for the CDMO's partners to advance their projects into clinical development in the most effective way.

A new project typically starts with a thorough analysis of product requirements from a clinical and commercial standpoint and goal setting. As a first step, the target product profile (TPP) has to be established. The TPP has emerged as an important tool that enables planning and communication between all key stakeholders, sponsors and regulatory authorities, and helps to establish the efficacy, safety and commercial suitability of the product. The US FDA issues guidance on the TPP for better communication between product developers and regulatory agencies.

The TPP for nanoparticles typically includes the following product characteristics:

- Dose – in the early stage it can be a range of doses that is further defined after dose-ranging clinical studies, typically in Phase II.
- Concentration of the final drug product (DP).
- Yields – the cost of the raw materials (both cargo and excipients: lipids, polymers) is very significant, so waste needs to be minimised.
- Stability – both chemical and colloidal stability need to be evaluated. Frozen product can be used for early-stage clinical trials to accelerate timelines but, for commercial products, a formulation stable at room temperature or 4 °C (refrigerated conditions) is much preferred.
- Container closure/presentation – single dose, multi-dose, vial and syringe or prefilled syringe presentation?

For multi-component systems, the process is critical, so it is very important to ensure control over the product properties, process robustness and reproducibility. A successful approach can best be described as "the product is the process", as control of the product properties is best achieved through the control of the process and the associated unit operations.

Key unit operations and critical process parameters must be defined early in the development process and include LNP batch fabrication formulation and downstream operations (Figure 3; DP unit operations, such as aseptic fill-finish, and labelling/packaging, are not included). In addition, robust analytical methodology needs to be established to ensure control of the process.

One of the key aspects of developing LNP-based formulations with the desired target properties is the composition. Typically, LNPs contain the following lipid components:

- Ionisable lipid, positively charged at low pH (enabling RNA complexation)
- Helper lipid that contributes to delivery efficiency and stability
- Structural lipid, such as cholesterol
- PEGylated lipid to minimise reticuloendothelial clearance and increase circulation time.

The development protocol and formulation of the LNP are achieved using design of experiments optimisation to balance efficacy and tolerability, and to ensure that the overall manufacturing process

is as effective as possible. This includes establishing robust and reproducible processes that can be scaled up or down, along with LNP drug product development incorporating formulation, stability studies and container closure comparability at an early stage.

As previously mentioned, robust analytical methodology must be established early in the development process. As per April 2018 FDA Guidance for Industry "Liposome Drug Products" this should include the following key test methods:

- Particle size
- Particle size distribution, PDI
- Zeta potential
- mRNA identity and concentration
- mRNA encapsulation efficiency (%)
- Lipid identity and purity
- pH and osmolarity
- Residual solvent
- Sterility (endotoxin and bioburden)
- Stability: 4 °C and/or frozen suspension
- Content uniformity (mRNA in the vial).

To date, the automated nanoparticle system has been used successfully to fabricate mRNA LNPs with controlled particle size between 80 and 150 nm throughout the process – scaling up and down without having to redevelop the protocol – a modest size increase post dialysis/concentration and mRNA encapsulation above 90%.

THE WAY OF THE FUTURE

Building on the success to date, there are now plans to develop a fully automated, lab-scale walk-away system able to generate libraries of 10 to 96 samples per run from precursor lipids and cargo, using septum-sealed 96-well plates to prevent cross-contamination and avoid evaporative losses. Predefined user data files uploaded to the system software will allow easy input of preparation protocols, including lipid and cargo selection, flow rates, in-line dilutions and heart cut sample collection, as well as the volume to be collected. The platform will enable collection of samples ranging in volume from 250 µL to 2 mL in sealed well plates, with a full system wash of all wetted parts between samples to ensure there is no cross contamination.

Once validated, this system will form the basis of a future modular high-throughput cGMP system incorporating sterilisable multiple multichannel microfluidic chips – typically offering a 100-fold increase in production throughput, compared with a single channel – and the capability to operate in continuous flow at up to 250 mL/min per channel to allow production at rates from 1–15 L/h per module.

CONCLUSION

Automated LNP production offers a seamless complete pathway from protocol development to GMP manufacture, without the need to change and revalidate methods. Researchers now have a tool for more effective, flexible and cost-effective protocol development and optimisation, as well as library generation, with better control of particle size distribution and encapsulation efficiency. Crucially, the process is scalable, by operating in continuous flow and by incorporating multiple microfluidic chips working in parallel, ensuring that the same method can be used from development right through to GMP production.

The authors believe that the commercial model for this development work should be "no strings attached". This means that the development work is fairly valued and paid for as it is performed, without a requirement for royalties after the product has launched. Royalty-based approaches add an additional barrier and commercial risk into the cost model, increasing costs for successful products and reducing the collaborative drive during the critical stages of the development process. Open access to the microfluidics platform and associated services would enable rapid and cost-effective development of the next generation of innovative nanoparticles products.

LNP development requires a strong collaborative effort between product developers and process engineers and the support of an experienced CDMO. It is vital that all key aspects of the product and process are evaluated, designed and built in early in the development cycle to avoid unnecessary development timeline delays.

ABOUT THE COMPANIES

Dolomite Microfluidics is a leading provider of microfluidics-based solutions aimed at helping its customers push the boundaries of science and engineering. Dolomite's systems and products are used in a wide range of applications, including drug development, chemistry, food and cosmetics, and in academia. Based in Royston (near Cambridge, UK), Dolomite is part of the Blacktrace group of companies,

a world leader in Productizing Science™, with offices in the US, Japan and Vietnam, and worldwide distributors offering technical assistance and support.

Phosphorex is a leading CDMO specialising in particle-based platforms such as LNP, polymeric microsphere and nanoparticle formulations with applications in the delivery of nucleic acids, sustained release and targeted drug delivery. Phosphorex offers tailored solutions and enabling technologies to optimise a drug's release rate, targeting ability, bioavailability and deliverability, with the goal of achieving desired therapeutic effects while reducing adverse clinical outcomes. Phosphorex supports pharmaceutical and biotech companies through all phases of their development, from proof of concept to clinical studies. Phosphorex's mission is to help its partners solve complex problems, shorten the time to clinic and develop successful drugs to help patients.

ABOUT THE AUTHORS

Richard Gray, MA (Cantab), is Commercial Director of Blacktrace Inc – the US office for the UK-based Blacktrace Group, which includes the Dolomite Bio and Dolomite Microfluidics brands. An engineer by training, his career started with five years working on advanced helicopter design at Westland Helicopters. Mr Gray transitioned to a wider range of technologies, including technical product development at PA Consulting (London, UK) and The Technology Partnership (Melbourn, UK), and worked on automated small molecule drug synthesis systems at Mettler Toledo (OH, US) before starting at Blacktrace in 2001. He is one of the two co-founders of Blacktrace, which was established 20 years ago to commercialise microfluidic technology for a wide range of scientific applications. Mr Gray's current activity is focused on using microfluidics for automated particle and nanoparticle generation.

Julia Rashba-Step, PhD, is a Vice-President of R&D and Alliance Management at Phosphorex. In her current role, she works closely with pharma and biotech partners to help advance cutting-edge, innovative technologies into critical programmes. Dr Rashba-Step is a senior pharmaceutical professional with an extensive background in biotechnology and pharmaceutical industries. She has experience working at both small companies (Epic Therapeutics) and global pharmaceutical companies, including Baxter, Wyeth and Pfizer, where she held positions of growing responsibilities, such as leading the Novel Delivery Technologies group at Pfizer. Dr Rashba-Step's technical background is in pharmaceutical product development, with a focus on drug product, advanced formulations and delivery aspects.

OVERCOMING DEVELOPMENT OBSTACLES TO THE DELIVERY OF EFFECTIVE OCULAR THERAPY

Here, Robert Lee, PhD, President of the CDMO Division at Lubrizol Life Science Health, discusses the growth of the ocular drug delivery market, the challenges formulators face in developing novel ocular technologies, and the role contract development and manufacturing organisations have to play in this growing market segment.

The global ocular drug product market was estimated to be worth US$36.7 billion (£26.3 billion) in 2020 and is set to expand at a compound annual growth rate 6.4%. One of the key reasons for this growth is an increasing awareness regarding eye-related diseases among the general public – not just in established markets but in a growing number of emerging economies as well.

From cataracts and age-related macular degeneration to dry eye and conjunctivitis, a wide range of conditions can afflict the eye, causing everything from minor discomfort to serious eyesight issues. The number of patients around the world seeking healthcare support for these conditions is growing rapidly.

This growth in the market is driving demand for advancements in therapies to treat a diverse array of eye conditions. Historically, the ocular therapy space has been focused almost exclusively on the development of topical treatments, such as eye drops and ointments. Such products have the advantage of being non-invasive but are not without their drawbacks. Topical treatments can only treat surface conditions, such as an ophthalmic allergic reaction, limiting the range of health issues they can tackle.

Traditional topical formulations also have disadvantages when it comes to patient experience. Standard eye drops, for example, often leak from the eye and drip down the cheek within moments of being administered. Not only is this messy and unpleasant for the patient, it means the dose can be removed from the eye before the API has been absorbed, undermining its effectiveness as a treatment and often resulting in the need for multiple daily administrations.

"Historically, the ocular therapy space has been focused almost exclusively on the development of topical treatments, such as eye drops and ointments. Such products have the advantage of being non-invasive but are not without their drawbacks."

As a result, the industry is moving towards more complex formulations and alternative dosage forms, such as injections and implants, to address the growing number of ophthalmic conditions.

RECENT OPHTHALMIC INNOVATIONS

A significant factor in the growth of the ophthalmic market has been innovations in treatments, including:

- Mucoadhesive topical formulations that have been designed to maximise retention at the target site, thereby extending active duration and allowing more of the API to penetrate.
- Long-acting injectables and ocular implants, which allow for extended drug release over a period of months or years. These enable the development of new treatments for more serious, long-term conditions, such as diabetic retinopathy.
- Drug-eluting contact lenses and intraocular implants that help to avoid leakage and dosing errors associated with topical applications.

With the potential posed by these innovations, it is no surprise that more and more pharma companies are exploring ocular drug products to provide better quality therapies for ocular disorder patients.

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"It is rare for pharma companies to have the infrastructure and expertise already in-house to develop ophthalmic products successfully on their own. Specialised expertise is needed to develop truly game-changing ocular therapies."

However, many companies face challenges when developing effective ocular drug products, from formulation issues to the choice of dosage form or delivery device, as many of these recent innovations are increasingly complex. This means that it is rare for pharma companies to have the infrastructure and expertise already in-house to develop ophthalmic products successfully on their own. Specialised expertise is needed to develop truly game-changing ocular therapies. To overcome these issues and ensure the successful development of their ocular therapy, drug formulators have several factors to consider.

KEY CONSIDERATIONS IN OCULAR DRUG DEVELOPMENT

Aseptic Processing

It is imperative that any ocular product is sterile to protect patients from infection, as the eye is sensitive and critical for sight. There are strict regulatory requirements in place with respect to sterility for ocular products, as opposed to other administration routes such as oral.

Dosage Form

The form that a drug product will take depends on the specific portion of the eye the API is intended to treat, as well as the desired dosing frequency. Conditions affecting the front of the eye are well-suited for topical formulations, including locally applied solutions, suspensions and emulsions. Retinal issues and conditions affecting the back of the eye are more suited to injections or implants. In these cases, to improve convenience for the patient, it may be preferable to develop long-acting formulations to minimise dosing frequency, and therefore also any discomfort experienced during administration.

API Challenges

The physical characteristics of the API must be factored into the ocular drug development process. The solubility of the API, for example, will affect numerous aspects, including which formulation techniques are used and what excipients are present.

OVERCOMING API SOLUBILITY OBSTACLES

No matter what dosage form is chosen for an ocular drug product, there are often challenges that need to be overcome during development to maximise the therapeutic effect of the finished product.

Across the pharmaceutical industry, more new chemical entities are being registered that exhibit poor solubility. This poor solubility poses challenges not only during the manufacturing process but also causes problems with the bioavailability of the API. Failure to address this issue when formulating the drug will have a negative impact on its effectiveness.

"However, there are other formulation approaches available that can help overcome solubility issues. Advanced technologies, such as API physical modification techniques, are particularly effective."

This challenge is particularly pressing in the ocular drug delivery segment. For example, there are few excipients approved for use in ocular dosage forms to help overcome solubility or bioavailability issues, especially for intravitreal administration. This restricts the avenues available to drug formulators to enhance the solubility of their APIs.

However, there are other formulation approaches available that can help overcome solubility issues. Advanced technologies, such as API physical modification techniques, are particularly effective. One example of this approach is nanomilling, which reduces the API particle size – increasing drug surface area and enhancing content uniformity along with dissolution rate. This can maximise the solubility of APIs that are moderately insoluble and allow for the formulation of highly insoluble APIs. As a result, the drug formulation may offer enhanced bioavailability and be able to achieve therapeutically relevant levels of the API within the target tissue or organ that would not otherwise be possible.

Additionally, nanomilling can create a more uniform colloidal suspension that offers enhanced application benefits – moving more effectively through the device or, in the case of a topical formulation, spreading more effectively across the surface of the eye.

Other techniques include additional physical modification methods, such as micronisation, and API chemical modification methods, such as PEGylation. Regardless of the method, it is important to focus on the drug product's target product profile and let science dictate the rest. Having more than one option or technique at your disposal is very important in the early stages of product development.

THE ROLE OF CDMOs

New technologies offer exciting avenues to both enhance patient convenience and compliance and optimise the effectiveness of drugs by improving the bioavailability of poorly soluble APIs. As more and more people are able to access ocular healthcare across the globe, we can expect patient demand for new and improved ocular products to grow.

To stand out in an increasingly competitive market, drug formulators will need to consider new ways of delivering their products and harnessing the benefits of the new generation of ocular dosage forms. At the same time, they will need to overcome the challenges standing in the way of successful ocular drug development – from bioavailability issues to aseptic processing and other manufacturing obstacles. As a result, contract development and manufacturing organisations (CDMOs) with expertise in this area will continue to play an important role in the development of novel ocular therapies.

ABOUT THE AUTHOR

Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development along with providing the company's strategic direction. Before joining Lubrizol, Dr Lee held senior management positions at Novavax, Lyotropic Therapeutics and Imcor Pharmaceutical Co. He holds BSc degrees in Biology and Chemistry from the University of Washington (Seattle, WA, US) and a PhD in Physical Bioorganic Chemistry from the University of California (Santa Barbara, CA, US). Dr Lee has published more than three dozen articles and five book chapters, as well as holding 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. Dr Lee maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas (Lawrence, KS, US) in the early 1990s, serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences, and serving on the Editorial Board for the journal MOJ Bioequivalence & Bioavailability, The Scientific Pages of Nanotechnology and the Journal of Analytical and Pharmaceutical Research.

ABOUT THE COMPANY

The Lubrizol Corporation, a Berkshire Hathaway Company, leverages its unmatched science to unlock immense possibilities at the molecular level, driving sustainable and measurable results to help the world Move Cleaner, Create Smarter and Live Better. Founded in 1928, Lubrizol owns and operates more than 100 manufacturing facilities, with sales and technical offices around the world and has approximately 8,800 employees.

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