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ONdrugDelivery Issue N° 110, August 31st, 2020

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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Sep 2020	Wearable Injectors
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Dec	Connecting Drug Delivery
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Apr	Pulmonary & Nasal Drug Delivery
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Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery

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APPLICATIONS OF DEEP LEARNING IN MEDICAL DEVICE MANUFACTURING

In this article, Frederick Gertz, PhD, Manager of Data and Process Innovation, and Gilbert Fluetsch, Director, Automation Systems, both of SHL, look at how deep learning can be leveraged in a medical device manufacturing environment.

As buzzwords go, few have had the effect that "deep learning" has had on so many different industries. When deep learning entered the industrial scene, there was much interest and success from companies in various industries. Technology companies such as Google, Microsoft and Apple have always had heavy investment in the area, while traditional pharmaceutical and healthcare companies such as AstraZeneca,[1] Novartis[2] and Pfizer[3] have also drastically increased their spending in areas related to artificial intelligence (AI).

During the early days, the techniques, benefits and limitations of deep learning were less known to most industries and, in particular, presented various challenges to the medical device and manufacturing fields with a somewhat "black box" connotation.

WHAT IS DEEP LEARNING?

The first struggle for industries exploring the deep learning revolution is to understand what deep learning is and how different it is compared with more traditional tools, such as machine learning and computer vision.

Machine learning is a subset of AI research and applications. In the 1960s, many algorithms and techniques were developed specifically for AI research, with the ultimate goal of developing a general intelligence. Unfortunately, many of the techniques fell painfully short of providing that level of capability.[4] However, several of the mathematical techniques were applied to a smaller subset of problems, such as handwriting recognition, image recognition, etc. – demonstrating great ability at optimisation and prediction within these domains. Even though some of these tools showed less promise for the development of general AI, they exhibited great potential for many less-aspiring applications. From this, the area of machine learning grew steadily.

In addition, machine learning tools such as principal component analysis (PCA), support vector machines (SVMs) and neural networks were used for a variety of tasks, usually focused on the problem of classification[5] and optimisation[6] of existing systems. Engineers in this field focused much of their time on feature engineering, which is simply different representations of data. For example, if a person wanted to track manufacturing performance, they might decide to calculate the average of a process dimension on a weekly basis. This would smooth out fluctuations and make it easier to objectively compare and determine long-term trends in the manufacturing process. Data scientists refer to this simple act of averaging the data as the engineering of a feature.

While data scientists typically develop much more complicated mathematical transformations, this example illustrates an important aspect of the process that machine learning engineers undergo when analysing a data set and building models. In fact, after data wrangling (the cleaning and organising of data to prepare it for processing), feature engineering[7] is one of the most time-consuming aspects of machine learning – and, in many cases, the most complicated.

So, how does deep learning differ from machine learning (Figure 1)? Deep learning

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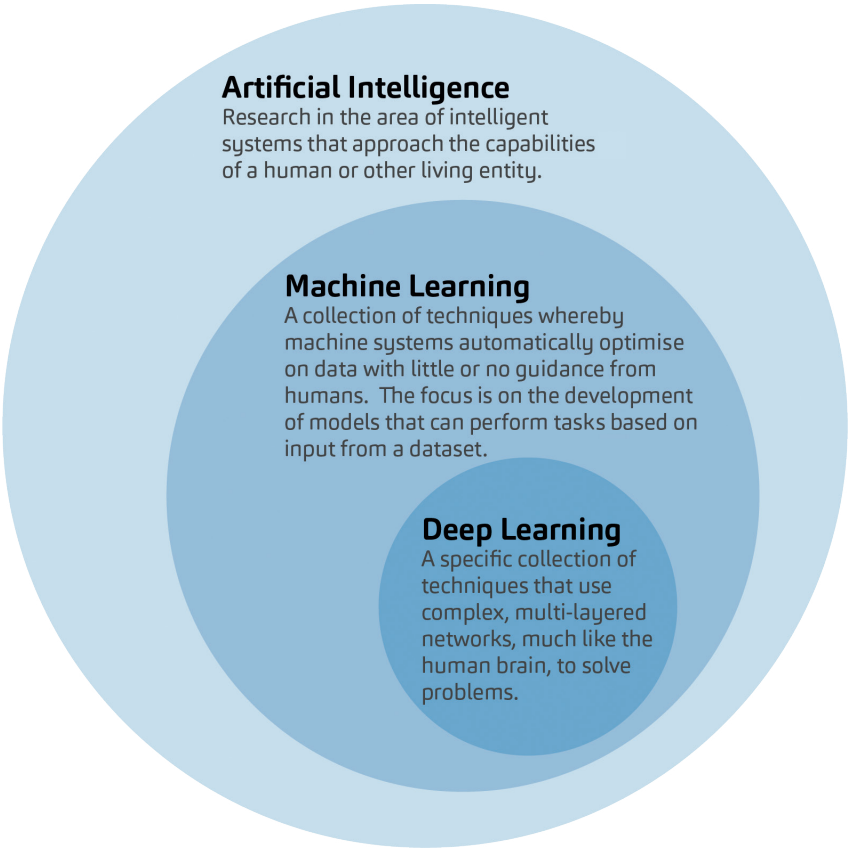

Figure 1: The relationship between AI, machine learning and deep learning.

takes some of the machine learning tools, such as neural networks, and expands their size, allowing them to learn iteratively without the need for "handcrafting" of features. Most importantly, for many applications, these networks require little or no feature engineering, learning on their own from "raw" inputs.

As with many scientific discoveries, the technique quickly expanded and the combination of much larger networks with extensive optimisation, particularly using graphical processing units (GPUs), led to the wider adoption of deep learning. In essence, deep learning can be characterised by two things – larger networks with more nodes,[8] as well as less emphasis on the need for humans to perform feature engineering.

APPLICATION IN MANUFACTURING ENVIRONMENT

Machine builders in the automation field of assembly equipment have been focusing for years on the mechanics of machines. Indexing, cam-driven mechanisms, pick and place, and mechanical grippers, etc. have been the primary description of the mechanical functions and processes of automated equipment. Project managers and mechanical engineers have been the driving forces behind these projects, often deciding how much control would be integrated into the equipment. Electromechanical components became available to increase the accuracy and also the precision of an assembly step.

For example, a standard assembly process from the past would be to use a pneumatic cylinder that would drive to a given distance. In the event of interference between two parts, the assembly process continues unless the force of the interference becomes higher than the force of the cylinder. But one could not control or monitor the assembly process. Today, servo motors with load cells are often implemented to achieve precise control of the assembly force, while also enabling engineers to get a read-out of force curves if needed.

> "The main challenge has been, and still is, not to define a component or measurement as good or bad – but to identify a criterion that lies between pass and fail."

This process is known as control engineering, a discipline that has gained much attention compared with just a few years ago. Although the mechanical process of an equipment is still important, more electronics and monitoring of assembly processes result in an increased need for control engineering talents in the development of said equipment. The integration of such different controls generates a wealth of data which can be leveraged by machine builders.

As customers and manufacturing operations push for increased cost-effectiveness and flexibility in manufacturing systems, these same requirements are also pushed onto the control engineers. The additional burden of these new requirements places a strain on all aspects of automation machine design and manufacture – but a particular strain is placed on control engineers, who are now turning to new fields, such as deep learning, to find faster, more flexible means of implementation.

DEEP LEARNING AT SHL

At SHL, we have been working with various machine learning techniques and exploring ways that they can be incorporated into our workflows and used to optimise our processes. In recent collaborations with our Automation Systems department, we repurposed a wealth of data and experience collected over many years of automating the manufacturing process. The Automation Department is a natural partner for the Data and Process Innovation team due to its mature implementations of robotics and computer vision systems, which have allowed for robust deployments and rich datasets.

In recent years, cameras and visual inspection systems have gained popularity as technology evolved. The main challenge has been, and still is, not to define a component or measurement as good or bad – but to identify criteria that lie between pass and fail. Historically, one of the most important components of an inspection system with cameras in an equipment was the lighting – direct, indirect, ring lights, etc. Light sources which "burn" out after a while resulted in an inspection that was no longer accurate.

The implementation of LEDs gave support in overcoming these challenges, while different LED colours were used for different applications. The colour of the LEDs can now be customised based on the

object and the inspection environment – and they therefore represent the ideal light source for the inspection project. Now, those LEDs are able to point out distinctive features on a component, such as angles or specific contours.

Nonetheless, the above does not account for the fact that complicated algorithms, usually hundreds or thousands of lines of code, had to be programmed for an inspection of a component, a measurement of a critical dimension or any other application. The code would often rely on pixel counts of the camera, which in turn was dependent on the resolution of the camera as well as the above-mentioned light source. Hundreds of hours of testing would follow the coding process and, even then, the traditional inspection systems would not provide solutions that could be trusted 100%.

There is an increased push for higher volumes of output with lower investments, necessitating the need to transition from manual assembly to semi- and fully automated assembly. These transitions, especially for products not originally designed for automated assembly, require a rapid collection of data and development of numerous control systems to provide accurate and high-quality assembly of parts. Frequently, this transition can lead to unexpected challenges as well as the need for additional design and inspection requirements to be incorporated into the production process.

One of the focuses of the Automation Department is the development and manufacture of large-scale, fully automated assembly machines. The machines provide SHL with the ability to drastically increase output for high-volume projects while also increasing consistency in the assembly process. At SHL, these machines frequently incorporate multiple vision inspection stations, all of which are enriched with unique data sets from our assembly and testing processes. The Data and Process Innovation (DPI) department investigated the use of deep learning in conjunction with some of these computer vision stations. Below we share an example and some results from one of our studies in the use

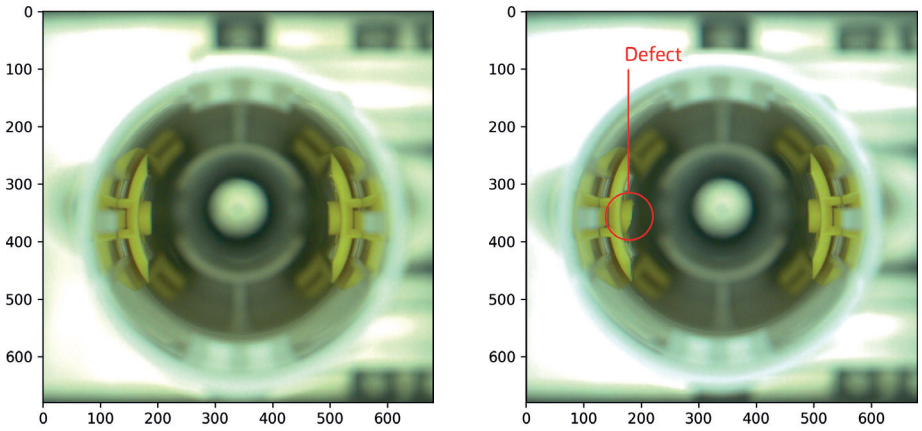

Figure 2: Two images showing a portion of a device assembly. This assembly is made from two parts, an outer white shell and a yellow insert. The left image shows an assembly that has been classified as good and the right image is an assembly that is damaged.

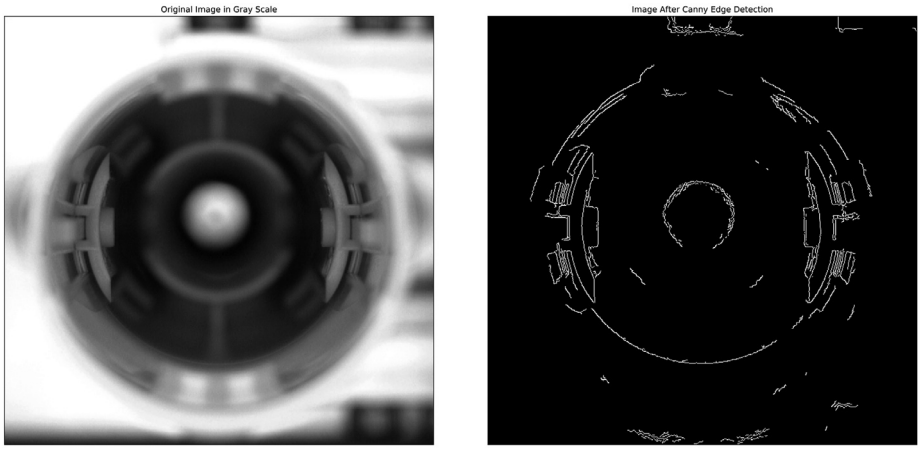

Figure 3: An example of an image after being processed with canny edge detection.

of deep learning for rapid vision inspection development and deployment.

A data set of images was provided to the DPI team for processing. Images were classified by human operators as either being good or bad (with or without defects). This assembly contains a front shell assembly (coloured white) and a yellow internal piece. As the piece is a functional part of the assembly, it is important that the moulded parts both fit together correctly and are free of any moulding or handling defects.

Figure 2 is an example of a good assembly (left) as well as an image of a bad assembly (right), with an annotation in the image to show an example of the defect. It should be noted that this is not the only type of defect; almost an endless possibility of defects could occur in the production and assembly of components. As such, multiple examples of different defects are required for training.

In a traditional computer vision set-up, the important areas of the images would first be determined through a combination of input from functional specifications and discussions with domain experts. Figure 3 shows the results of a canny edge detection, which would normally be used to reduce the data input into the computer vision algorithm. From this point, an engineer would define the areas of greatest interest and create rules which would be used to determine which parts are within specification and which parts contain defects.

It should be noted that during this process, a certain amount of interpretation is required from the vision engineer. Depending on the part, the process can be quite time consuming, requiring multiple iterations and several validations and revalidations. The technique, like all computer vision techniques, is sensitive to environmental changes and can pose a

"There is an increased push for higher volumes of output with lower investments, necessitating the need to transition from manual assembly to semi- and fully automated assembly."

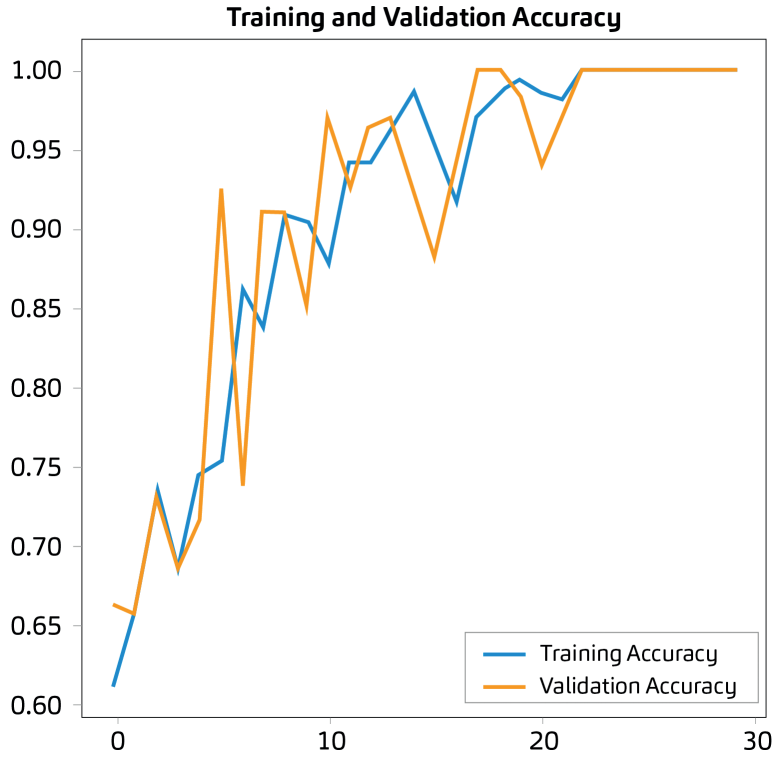

Figure 4: Graphical results showing the evolution of the TensorFlow convolution neural network over 30 iterations. The network uses two sets of files – a training set which the network learns on (blue line) and a validation set which the network tests itself against.

> "The ability of the deep learning algorithm is entirely dependent on the input data it receives and, as such, the most time-consuming aspect for some operations would be the data collection and labelling."

significant risk to the timeline in delivering automated equipment to the end users in manufacturing.

In comparison, we now show the results of the deep learning implementation. The deep learning implementation uses a convolutional neural network through the TensorFlow framework[9] – an open source, readily available tool for deep learning. The convolutional neural network was defined with the following basic parameters: a convolutional network with nine layers, including three convolution layers and three pooling layers. This network has a total of 236,773,409 parameters, which are all trainable. After defining the network, the images are provided to the network for training, without the need for any transformation like the above-mentioned canny edge detection. Using an unimpressive amount of computational resources, including a readily available laptop, the training over a data set of about 240 images took approximately 30 minutes.

According to the results (Figure 4), it is apparent that the network was able to learn quite readily on the images and reach 100% accuracy on the training data set. A test set of images was prepared to check for overtraining and, similarly, 100% accuracy was reached on the test set. Thus, with 30 minutes of work and a relatively small amount of data, the algorithm was able to provide a very high degree of confidence in its ability to segregate good images from bad.

This technique undoubtedly scales up quite nicely, with new defects easily added to the data set, which can even include difficult-to-define cosmetic defects as well. The ability of the deep learning algorithm is entirely dependent on the input data it receives and, as such, the most time-consuming aspect for some operations would be the data collection and labelling. As a long-time manufacturer and user of automation equipment, SHL has an abundance of validation and production data on hand, which gives us the unique ability to leverage the development of data-intense models such as those used for deep learning algorithms.

LEARNING FROM DEEP LEARNING IMPLEMENTATIONS

This sort of implementation is far from cutting edge, and the example shown does not include the multiple additional steps required to help train for robustness and test the network. However, once the model is developed, production and validation will need relatively strong assurance that it is performing at a high level. At this point, some interpretation of the model becomes very desirable.

Despite the reputation of deep learning models, as mentioned previously, there are avenues that can be used to gain insight into the performance of the model.[10] For example, one common technique used by deep learning engineers who work with images is to have heat-map overlays produced on the images (Figure 5). In these examples, a heat map is created to show regions that the neural network has, through its training, identified as important.

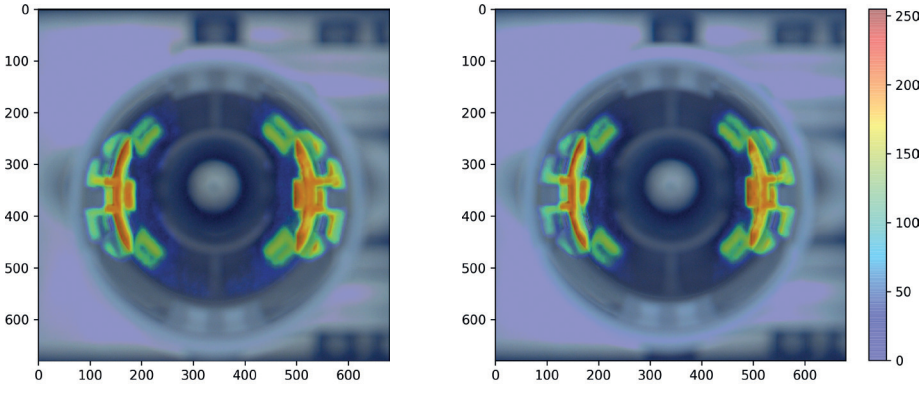

Figure 5: Images from Figure 2 are overlaid with a heat map where the neural network identifies areas of interest based on its training.

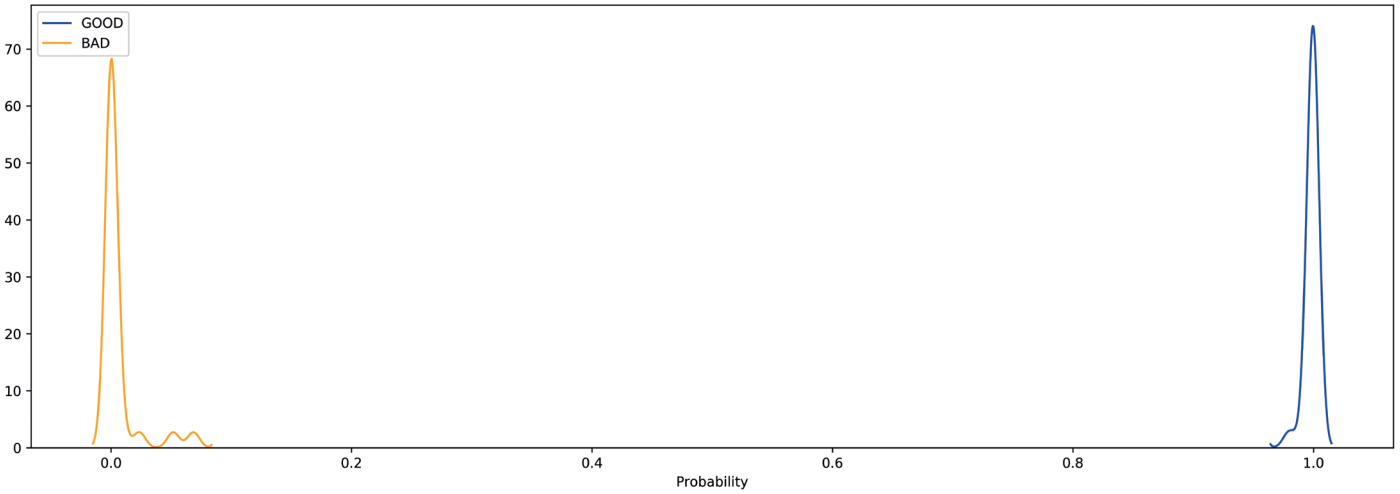

Figure 6: The distribution of good and bad samples, based on results from the neural network. Good samples (coloured blue) show a clear distribution completely opposite to the distribution of bad samples (orange colour).

In the images below, it is clear that the network has correctly defined the areas of importance. It is able to identify that the yellow plastic insert is the region of interest and even shows that the edges of the yellow insert are of even greater importance, performing what can also be viewed as a type of edge detection.

Images such as these can give production engineers a greater deal of confidence that the regions of interest correctly overlap with the areas the production or control engineers would have selected as being the most important. Furthermore, the network does not give a purely binary output. In fact, we can ask the system to provide a continuous probability outcome. In this case, the system assumes that a perfect sample would be scored a one and a bad sample would be scored a zero. We can obtain the distribution results shown in Figure 6, which represent the results for the validation data from the final iteration of the TensorFlow model's training.

We can see from these results that there is a distribution with a strong centre for good samples (blue) at about 0.99 and a strong peak for bad samples (orange) at about 0.02. If we were to evaluate this system as we would many other measurement systems, we could perform a typical statistical analysis and would conclude that even the edge cases of this measurement are quite far removed from the classification boundary of 0.5.

Herein lies another advantage. The 0.5 limit is somewhat arbitrary. It assumes that if the system classifies the part as more likely in one category from another, then that is where it places the classification tag. However, in production, especially risk-averse production such as medical devices, we can tighten the criteria to 0.8 or even 0.9, telling the system that it must be absolutely certain in its classification; otherwise it should reject the part. With a stricter criterion, we have the ability to not only test and validate the system similar to any other measurement system, but also to move criteria based on our own risk assessment and requirements.

> "We have the ability to not only test and validate the system similar to any other measurement system but also to move criteria based on our own risk assessment and requirements."

CONCLUSION

SHL continues to advance its understanding of the development and validation of these techniques as we explore their deployment into our production processes. Real-world examples derived from internal SHL investigations demonstrate how deep learning can be leveraged in a medical device manufacturing environment. The findings are quite surprising. First, the amount of training data is smaller than might be thought from other deep learning applications.[8] We assume this is because of the high consistency that is required in the manufacturing environment, resulting in faster learning of the underlying data distributions. Second, the interpretability, the ability of the model to relay parts of its process to engineers, is quite a bit higher than is expected from a true black box.

With these learnings in mind, and with the speed and robustness that these types of techniques offer, SHL expects to see further adoption of deep learning models in manufacturing, both internally and amongst the medical device manufacturing community as a whole.

ABOUT THE COMPANY

SHL Group is a world-leading solutions provider in the design, development and manufacturing of advanced drug delivery devices such as autoinjectors, pen injectors and advanced inhaler systems. It offers a full range of in-house core competencies and services in the fields of medtech and patient care. With >4,000 employees worldwide, SHL Group consists of several distinct group companies: SHL Medical designs, develops and manufactures advanced drug delivery devices for leading pharma and biotech companies across the globe; SHL Healthcare develops and manufactures equipment solutions for home, hospital and long-term care use; and SHL Technologies provides contract manufacturing and engineering services for the production of complex medtech products.

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ABOUT THE AUTHORS

Frederick Gertz is the Manager of Data and Process Innovation at SHL Medical. His focus in the company is on facilitating data-driven methods across the organisation and providing unique insights from data using a variety of techniques, including artificial intelligence and deep learning. Prior to SHL, Dr Gertz worked in the medical device start-up space where he focused on bringing novel processes and techniques, including machine learning, into the biotech industry. He holds a PhD in Electrical Engineering from the University of California, Riverside (US) where his research focused on biophysics and spintronics.

Gilbert Fluetsch joined SHL'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 in various leading roles in engineering, operations and sales management in the medical device and semiconductor industries for almost three decades. He has an MBA in High Technology Management from the University of Phoenix (AZ, US) and a BS in Business Administration from California State University San Marcos (US).

AARON MANN, CHIEF EXECUTIVE OFFICER, KINDEVA

Aaron Mann is the Chief Executive Officer of Kindeva Drug Delivery and was previously President and General Manager of 3M Drug Delivery Systems. He holds a BA in Economics from Carleton College and an MBA from the Harvard Business School.

In this exclusive interview with ONdrugDelivery, Aaron Mann discusses how Kindeva is positioned to move forward as a major CDMO specialising in inhalation and transdermal (passive and microneedle-based) dosage forms, having been formed in May 2020 when Altaris Capital Partners acquired 3M's drug delivery business for US$650 million (£496 million). We discuss the divestment and Kindeva's formation, and how the new company represents a valuable opportunity to meet today's challenges, building on the organisation's legacy experience, track-record and capabilities, whilst also innovating in new directions and developing new interesting ways of doing business and working with partners. We also cover the impact of Covid-19, environmental sustainability, and current challenges faced by the pharmaceutical industry.

Q Congratulations on your appointment as Chief Executive Officer of Kindeva Drug Delivery at its formation. Can you describe Kindeva in terms of how it is positioned, broad mission and strategy, key elements of the business offering?

A Well, thank you – it's really a privilege. We have such a remarkable team and Kindeva represents an amazing opportunity to help drive our customers' success.

So, Kindeva is one of the larger leading CDMOs globally, with a particular focus on complex drug and combination products. Our passion is helping our customers realise the whole potential of their programmes.

Our capabilities today reflect our depth of expertise in formulation, in development and through to manufacturing. Customers engage us at all stages along the development continuum. We take in an API from our customers and when they return they are collecting commercial batches from us, for marketing and distribution. We offer a global turnkey capability.

Historically, we've been focused in the inhalation space and we are well known for a lot of pioneering work around metered-dose inhalation. We also have considerable experience across different delivery technologies including in the transdermal space with patches and drug-in-adhesive systems. And increasingly we work with active transdermal systems and microneedle-based platforms.

> "We have a track-record with regulatory authorities throughout the world. The fact that it's integrated right within the business, sitting side-by-side with the labs and manufacturing as opposed to residing in a third-party consultant, brings a further level of benefit. This minimises risk for our customers."

We draw on our deep experience and integrated capability set from early development through to manufacturing, so from a project's outset we're able to think through all the factors at play, the trade-offs, and the implications of different choices, which are different in each of the delivery routes.

Figure 1: Kindeva is developing smart, connected drug delivery solutions.

Kindeva is a new name, a new entity, but the reality is that we have extensive, deep and unique experience having helped our customers develop a large number of products through to market. We have a track-record with regulatory authorities throughout the world. The fact that it's integrated right within the business, sitting side-by-side with the labs and manufacturing as opposed to residing in a third-party consultant, brings a further level of benefit. This minimises risk for our customers – their programmes' chances of success are increased.

Innovation is a core part of our DNA and as Kindeva we're accelerating our innovative capabilities, continuing to engage with customers around inhalation, transdermal and microneedle technologies, and delivering solutions around smart and connected devices (Figure 1).

Ultimately, we're focused on helping our customers help their patients. Fundamentally that is the need. Kindeva can help people receive the therapy that's important to them.

Q Could you outline the role of Kindeva's products and services during the coronavirus pandemic? And how is the company navigating this period affected by the outbreak in terms of operations?

A The focus that my management team and I have every day is on our people. We can only make the best contribution if we are really taking care of our people. You saw that reflected in our culture before the transaction as well, so we're certainly benefiting from bringing that culture with us – helping our people take care of themselves and take care of each other. Many of our folks have needed to be in the labs and factories to keep these essential projects going throughout the pandemic, as our business is defined as an essential industry. And our teams in our manufacturing facilities, in our supply chain, in our labs, they've done a terrific job.

In terms of the role of Kindeva's products during the coronavirus outbreak, a number of our products and of our customers' products, are playing really important roles. First, with the inhalation space being one of our core areas and Covid-19 being a disease that affects the respiratory system, the applicability is self-evident. Inhalers are always important when you're dealing with a respiratory disease. We're hearing from our customers that the need for inhalers is growing.

There have been some concerns about nebulisers potentially generating droplets capable of spreading viral matter so there's been a move away from nebulisers in some hospital settings and alternative devices such as MDIs are used. This increases underlying demand for us. Also, some of the inhaled products that we make have been investigated for potential efficacy against Covid-19 symptoms.

> "I think it's a testament to everyone who was engaged in it that we were able to complete the process despite the coronavirus outbreak."

Figure 2: Kindeva's hollow Microstructured Transdermal Systems (hMTS) are designed for intradermal delivery of vaccines and biologics.

We've played a role in helping pioneer microneedle platforms for intradermal delivery (Figure 2), and this delivery route can trigger a very strong immune response. Our customers have been working on cancer vaccines and immuno-oncology for some time and so the question becomes, does this delivery approach have potential for a SARS-COV-2 vaccine?

One of the further benefits of microneedles is of course that they allow self-administration which would have significant advantages for the kind of mass vaccination programme required for coronavirus compared with requiring a healthcare practitioner, for each and every person being vaccinated, to go to a refrigerator, take a refrigerated dose and inject it. If we're able to come up with something that's self administered, the ability to get it out across the globe and achieve the immunity across populations that is required, could be heightened.

Q The coronavirus outbreak struck just as the divestment of Kindeva from 3M was taking place. How did it affect the process?

A I think it's a testament to everyone who was engaged in it that we were able to complete the process despite the coronavirus outbreak.

The team at Altaris have been terrific partners. Their conviction around the drug delivery space, and their experience with these kinds of transactions have been invaluable as has their support for the team that leads the drug delivery business. That team did not miss a beat running the business while simultaneously working to-plan on the divestment, all with a virus outbreak happening at the same time.

> "The team did not miss a beat running the business while simultaneously working to-plan on the divestment, all with a virus outbreak happening at the same time. Everyone involved just kept up the momentum, never doubted that this was absolutely the right thing to do, and there was a collective sense that we'd dip our shoulders and get it done together. And that's what we did."

Everyone involved just kept up the momentum, never doubted that this was absolutely the right thing to do, and there was a collective sense that we'd dip our shoulders and get it done together. And that's what we did.

Q Staying with the transaction, can you describe what is included in the transaction and how Kindeva will be able to stand-up on its own?

A There is immense opportunity with the drug delivery business, but

the best way to realise that was with someone else investing behind it. Notice that 3M is retaining a 17% stake in the company. As opposed to having any lack of conviction about the industry, they do see the opportunity.

In terms of what comes with the divestment, it is the core of the business; the vital parts of what we do. First and foremost, this means all of the people. If you look at the business from the top down, the Kindeva leadership is the same leadership team that was running the drug delivery business at 3M. Even more importantly, our technical whizzes, our regulatory experts, our R&D teams, both in the US and in the UK where we have a large footprint. Those people and those labs are part of the transaction as is our terrific manufacturing infrastructure, again both in the US and the UK. Also included is the technology, the IP that underpins what we do.

From the point of view of our customers, in some respects it is just a change in name. They're interacting with the same people, at the same plants, the same products, the same capabilities at Kindeva as they were when the business was part of 3M.

We've had tremendous support with regard to the transition to enable fast and responsible decision making to achieve a very thoughtfully planned separation ensuring that Kindeva stands on its own two feet.

Q How do deals like this affect employees? Do patients benefit ultimately?

A I've been impressed by the amount of energy generated with our people by this opportunity to really take ownership of our culture of the direction of driving the business. It is different when you're part of a much larger multinational. As Kindeva we have the ability to, for example, make faster decisions around how we're going to invest in growth, what we're going to put our efforts and energy behind, where we're going to choose to innovate. That gets our people more involved and energised, and we can envisage achieving beyond our already very high level of achievements within 3M. Accelerating the innovations that go into development and getting better products out faster – clearly this ultimately leads to patient benefits.

> "We'll have the ability to make faster decisions around how we're going to invest in growth, what we're going to put our efforts and energy behind, where we're going to choose to innovate."

Q Could you describe Kindeva's customers? What are the challenges they are facing and how can Kindeva help them overcome current challenges?

A Our customers include large global biopharma players, particularly those who have historically focused on inhalation in asthma and COPD, and have more recently been tackling other disease states via the inhalation route. And at the other end of the size spectrum we have quite a number of smaller / start-up companies, for example in the immuno-oncology space and other complex vaccines. Here there is a lot of translational research, developments out of universities and so on. So we work globally and with companies of all sizes.

In terms of the challenges our customers are currently facing, clearly in the near term they are all considering the coronavirus outbreak and its aftermath. That's going to impact each of them differently dependent on their portfolios and their footprints. As a CDMO, Kindeva is there to support them as they navigate these obstacles.

More broadly, pharma is of course being challenged by the increasing costs and risks involved with successfully developing and commercialising a product. We all read in the press what the cost of a success is, how it's rising, how the timeline is stretching out and how big pharma companies are facing challenges around capital and resources allocation.

In some ways that makes it just the right time for us to be establishing Kindeva as an independent company, as an even stronger partner to those customers. What we're capable of doing in terms of services at the complex end of the industry is in many instances exactly what they are looking for – partners with the expertise, the experience and the track-record to take on these difficult challenges and deliver successful products.

With more biologics coming through, and the increase in emphasis on the patient, looking into adherence and compliance, a company that's focused on drug delivery and development really can add value, for example by solving usability challenges, identifying failure modes, and the challenges of ensuring patients use their devices properly so that their therapy is effective. These things can sometimes seem quite simple to us, but not getting it exactly right and not providing the right technology and associated support to help a patient self-administer, can create a gap between what you expect to be the therapeutic outcome and the actual outcome.

Across the industry today, and especially in the inhalation field, environmental sustainability is a major consideration. Obviously as a major MDI manufacturer, sustainability is something that Kindeva is thinking deeply about and has policies on.

Our team has been addressing environmental issues for many years, all the way back to the transition from CFCs to HFAs and the Montreal Protocol. We played a significant role in helping customers migrate to HFAs then and, although we're not quite ready to share details yet, our team has been working on what the next generation looks like when it comes to reducing the environmental footprints of devices. We're also looking to develop the conversation beyond the environmental impact of a single device, to look at therapies that are more effective or easier for patients to use, including at home, and therefore patients get healthier faster and reduce their environmental footprint in other ways. It's a complex conversation but an important one. As Kindeva, we intend to play our part. Our teams have a deep understanding of all of this, and this is a terrific asset for our customers.

Q What Kindeva product/technology/service offerings will facilitate its growth?

A Our core activity will remain working to help our customers tackle challenges in inhalation and both active and passive transdermal delivery, including microneedles. Our conversations with customers are as much about the capabilities that we have and how we can use those capabilities to help them, as

> "Obviously as a major MDI manufacturer, sustainability is something that Kindeva is thinking deeply about and has policies on."

about the technology platforms with which we are most experienced.

As you can imagine, the formation of a new company marks a time for renewal, taking stock and thinking about new, different, better ways of doing things. It leads to us and our customers thinking about the possibilities of partnering and working in ways that perhaps we were not accustomed to whilst part of 3M. Those exciting sorts of conversations are already starting with our customers.

From December 2019, when 3M first announced the intention to divest the drug delivery business, support from our customers has been unwavering. Of course, they had questions, in particular about whether the new business would comprise the same people. And when we reply, "Yes, absolutely", they have been delighted. It's exciting to have this rush of inbound interest in Kindeva and dialogue with our customers. They see the same opportunities that we do.

ABOUT THE COMPANY

Kindeva Drug Delivery is a CDMO offering its partners integrated, end-to-end capabilities spanning formulation, product development, scale-up manufacturing and commercial manufacturing. Its full-service innovation offering covers: inhalation (pMDIs, DPIs, connectivity, nasal delivery); transdermal delivery (drug-in-adhesive systems, membrane systems, reservoir systems, gel patches); and intradermal delivery (microneedles based on solid and hollow microstructures). Kindeva Drug Delivery has locations in the US and the UK and employs over 900 people. It was formed in 2020 when 3M's Drug Delivery Systems business was acquired by Altaris Capital Partners for US$650 million, and renamed Kindeva. 3M retains a 17% minority holding and Kindeva benefits from its 3M heritage comprising >60 years' pharmaceutical development, commercialisation and contract manufacturing services experience across inhalation, nasal, transdermal and microneedles.

Kindeva DRUG DELIVERY

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FROM FORMULATION TO MANUFACTURING: LIPID NANOPARTICLE mRNA VACCINES, GENE THERAPIES & OTHER NANOMEDICINES

In this article, Stephen Allan, Health Care Communications at Evonik, reviews the history and formulation advantages of lipid nanoparticles (LNPs) and addresses factors that should be considered by pharmaceutical companies during the CDMO selection process to help reduce regulatory risk, improve product performance and accelerate speed to market.

INTRODUCTION

> "LNP-based formulations have become the gold standard for the development of many complex parenteral products... Of the almost 20 LNP-based drug products that have been approved since 1995, around half have received the support of Evonik's team."

Lipid nanoparticles (LNPs) have received significant attention in recent months due to their use as the preferred delivery technology for several messenger RNA (mRNA)-based vaccine candidates that are being developed for the prevention of COVID-19. The ability of lipid nanoparticles to encapsulate genetic material including mRNA, as well as a range of other biologically active agents, for controlled delivery to a target cell or organ site, has now been clinically proven over almost 30 years of commercial use. This long history of clinical performance, together with their ability to be rapidly developed and scaled-up into a finished product, has made LNPs the *de facto* standard for gene- and cell-based therapies and other nanomedicines. In addition to mRNA vaccines, LNP-based formulations have become the gold standard for the development of many complex parenteral products such as anticancer agents, antibiotics, drug combinations and personalised medicines.

Of the almost 20 LNP-based drug products that have been approved since 1995 (see Table 1), around half have received the support of Evonik's team for advanced drug delivery.

The development of gene-based therapies, such as mRNA vaccines and other nanomedicines, requires the use of delivery technologies that are not only safe and efficacious, but simple to customise and efficient to manufacture. Such technologies must also be able to penetrate target cells effectively and ensure release for reliable systemic or local delivery. While delivery systems involving siRNA-conjugates have received some attention for use with a few highly specialised application areas, the overwhelming majority of non-viral formulations developed to date for gene therapies, cell targeting and other nanomedicines have leveraged LNP drug delivery technology.

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Product	Year Approved	API
Doxil®	1995	doxorubicin
Daunoxome®	1996	daunorubicin
AmBisome®	1997	amphotericin B
Visudyne®	2000	verteporfrin
Definity®	2001	octafluoropropane
Myocet®	2002	doxorubicin
DepoCyte®	2002	cytarabine
DepoDur®	2004	morphine
Mepact®	2009	mifamurtide (MTP-PE)
Exparel®	2011	bupivacaine
Marqibo®	2012	vincristine
Onivyde®	2015	irinotecan
Vyxeos®	2017	cytarabine and daunorubicin
Arikyce®	2018	amikacin
Onpattro®	2018	patisiran
Generic Doxil (Sun Pharma, Dr. Reddy's)	2001/2013 (Sun);	doxorubicin

Table 1: Liposome-based products approved since 1995.

Cell membranes are largely composed of lipids, which possess amphipathic qualities, whereby molecules contain one part that is water insoluble and another that is water soluble (Figure 1). While such molecules can be dried as powders or oils, they can be easily rehydrated in water whereby they self-assemble into higher-order spherical vesicles known as liposomes. These naturally occurring cellular processes are emulated in drug delivery systems that are capable of entrapping and retaining therapeutic or diagnostic agents within the liposome (Figure 2).

Lipid particles can be reliably processed via extrusion or micro-mixing systems into vesicle sizes down to, and in some cases even below, 50 nm. Furthermore, they can be precisely tuned to release the product payload at a rate that is therapeutically optimised for the silencing of targeted genes or the expression of therapeutic proteins. LNPs can also be tailored to exhibit specific physicochemical properties, such as particle size and surface charge, to satisfy a variety of functional requirements.

The Clinical & Commercial History of LNPs

Virtually any biologically active agent has the potential to be formulated with LNPs including hydrophobic drugs, small molecules, proteins and peptides, oligonucleotides and mRNA (Figure 3).

This ability for LNPs to encapsulate and protect a payload against degradation, while safely enhancing biodistribution and solubility characteristics, was first applied in highly potent compounds. Examples include intravenous administration of oncology drugs to help increase particle accumulation at the site of a solid tumour. These initial studies led to the approval of the first commercial LNP-based anticancer drug, Doxil, (doxorubicin, J&J) in 1995. Several other small-molecule drugs have been approved subsequently for oncology applications using LNPs to encapsulate and transport active molecules.

Of the almost 20 LNP-based drug formulations that have now been approved for human use (Table 1), most feature relatively simple formulations where the role of the LNP is to provide sufficient protection and stability so that the drug can be retained in the circulatory system and mediate controlled release at the target delivery site.

Figure 1: A liposome encapsulating an aqueous core and a bilayer consisting of hydrophobic acyl chains.

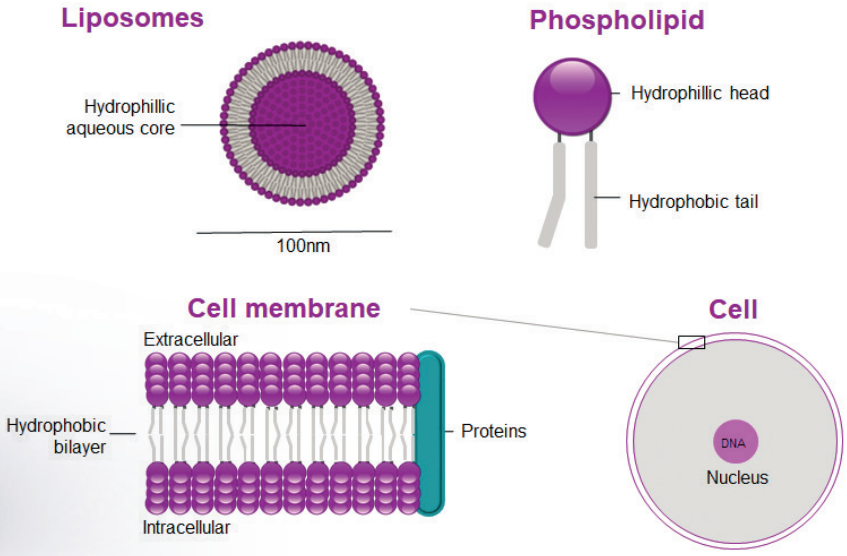

Figure 2: Liposomes mimic naturally occurring and highly stable vesicles featuring a cell-like morphology and high biocompatibility.

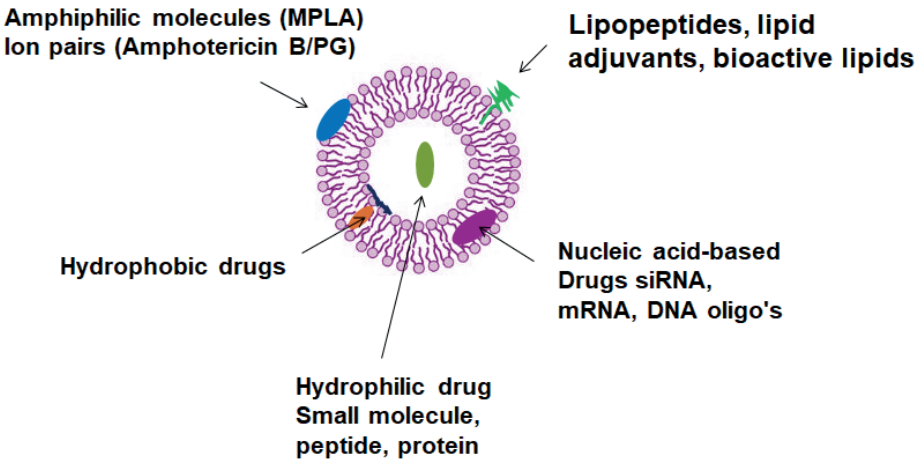

Figure 3: Liposomes provide excellent formulation versatility.

However, the potential of LNPs to deliver specialised or personalised drug products attracted significant industry attention in 2018 following the approval by the US FDA of Alnylam Pharmaceuticals' Onpattro® (patisiran lipid complex injection) for the treatment of polyneuropathy in people with the rare disease hereditary transthyretin-mediated amyloidosis. Onpattro® ushered in a new era of medicines collectively referred to as non-viral gene therapies.

In the case of Onpattro®, LNPs are first used to stabilise and then deliver small nucleic acid fragments known as short interfering RNA (siRNA) into the cytoplasm of the target cells in the liver. The delivered siRNA molecules then promote the degradation of a specific mRNA molecule. By decreasing the amount of mRNA, the ability of the cell to produce that specific protein within the liver is impaired. Such processes represent a new area of therapeutic intervention where faulty or over-expressed proteins can trigger certain genetic diseases, and decreasing their expression has therapeutic benefit.

Developing LNP-Based Formulations for use With RNA Applications

Biological fluids can rapidly degrade "naked" RNA molecules before they reach the target site. LNPs therefore play a vital role in encapsulating and protecting these highly active, but easily degradable, payloads until the target tissue is reached, thus ensuring the silencing of specific genes or the expression of therapeutic proteins. When properly formulated and manufactured, LNP-based formulations for RNA applications can significantly increase the effectiveness of delivery to the target site and the corresponding rate of cellular uptake.

One of the key considerations taken in the development of an LNP-based formulation with specific functional properties is the composition of the lipid components. For example, ionisable cationic lipids are generally responsible for maximising the intracellular delivery of the nucleic acid and play a role in payload encapsulation. The length, level of unsaturation and linker moiety of the hydrocarbon chains and pK values for the lipid are other factors that can influence potency and efficacy.

Another key component in determining LNP functionality is the incorporation of polyethylene glycol-lipids (PEG-lipids), which are comprised of a polymeric PEG chain and two hydrophobic lipid tails. These PEG lipids play a vital role in particle formation and storage stability. More importantly, they help prevent particle aggregation, modulate interactions with blood proteins and prevent rapid degradation by the immune system.

Manufacturing Methods for LNP-Based Formulations

The typical manufacturing process for liposome formulations is comprised of four steps that can be summarised as: formation, size reduction, purification and sterile filtration. The initial formation of the crude liposome suspension and its size reduction can be achieved most reliably via either a solvent dilution process followed by extrusion or microfluidic (micromixing) processes, which is a single-step process to achieve target nanometre size ranges. Extrusion is a pressure filtration process, where aqueous suspensions of lipids are forced through filters with a defined pore size, optimised for size reduction and high trapping efficiency. LIPEX® extruders have been the industry standard in this regard for more than two decades and range in scale from benchtop to commercial production for liposomes encapsulating various payloads including small molecules, proteins and peptides (Figure 4).

However, while such extrusion-based processes are preferred for many liposomal formulations, their application for use with mRNA and other nucleic acid systems has proven to be challenging. Increasingly, the most popular process for mRNA-LNP synthesis involves rapid mixing whereby a water-miscible organic phase containing

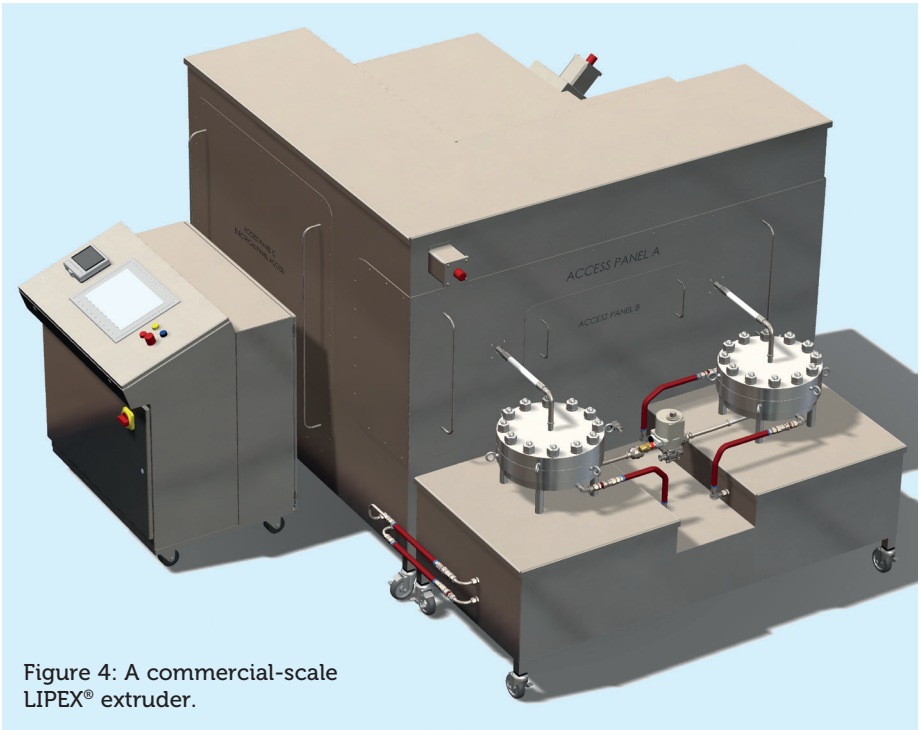

Figure 4: A commercial-scale LIPEX® extruder.

"Given the highly specialised nature of developing LNP-based drug products, it is common for pharmaceutical companies to partner with CDMOs that have established core competencies and a proven record for performance within this technology area."

the lipid components is mixed at dilute concentrations with an acidic aqueous solution containing the nucleic acid. A typical micromixing system consists of a set of pulse-free pumps and a mixing unit such as a T-connector or microfluidic chip. All micro-mixing systems require large in-process volumes and must operate at high flow rates to avoid long process times.

Following size reduction, purification typically occurs with tangential flow filtration systems to remove solvents, as well as any un-entrapped materials and buffer exchange. A clarifying step through a filter is then carried out for bioburden reduction, and also to remove any larger particles (>0.2 µm). As a final step prior to aseptic filling, sterile filtration commonly occurs through 0.2 µm filters to narrow particle distribution further.

Future Applications for LNPs

LNPs are now widely accepted across pharmaceutical and biotechnology industries as an advanced and commercially proven delivery system that is enabling the commercialisation of gene therapies on an unprecedented scale. Accordingly, LNPs have helped to herald the arrival of a new era of medicine where genetic diseases can be effectively treated or cured, and where vaccines can be produced within the body rather than by the purification of non-infectious viruses. Significant opportunities exist for LNP-based formulations to create drug products for protein replacement therapy, for preventative or curative vaccines and for gene editing purposes.

In addition to RNA, DNA and siRNA-based therapeutics, LNP-based formulations are being increasingly considered for use across a variety of other application areas including anticancer agents and antibiotics, peptide and protein-based synthetic vaccines, ligand-targeted formulations and imaging contrast agents.

Over the coming decade, LNPs are also expected to enable the development of even more complex nanomedicines. Examples include the development of drug combination products, synthetic vaccines or immunotherapies where LNP-based formulations are required to ensure the co-presentation of multiple components into the target cell. Additional opportunities include combining LNPs with tissue sequencing and other functional technologies to help create personalised or custom-made formulations that can enable outcomes such as the insertion of tumour-associated neo-antigens into mRNA vaccines.

Critical Factors in the Selection of a CDMO Partner for LNP-Based Drug Products

Given the highly specialised nature of developing LNP-based drug products, it is common for pharmaceutical companies to partner with contract development and manufacturing organisations (CDMO) that have established core competencies and a proven record for performance within this technology area. Such strategic partnerships may not only span formulation and process development activities, but also the clinical and commercial manufacturing of the finished product. Accordingly, it is important that CDMOs have significant expertise for the manufacturing of LNP-based formulations.

Prospective CDMO partners should be able to provide the customer with non-confidential demonstrations of how they have been able to help a customer deliver project outcomes within either the same or an equivalent application area. For mRNA or other nucleic acid-based projects, such case studies may include the successful development and production of formulations that ensure a payload is not degraded until arrival at the target site. Other demonstrated project outcomes may include increasing the solubility of lipophilic APIs, reducing systemic toxicity, or enhancing biodistribution as well as cellular and tissue uptake.

"LNPs are now widely accepted across pharmaceutical and biotechnology industries as an advanced and commercially proven delivery system that is enabling the commercialisation of gene therapies on an unprecedented scale."

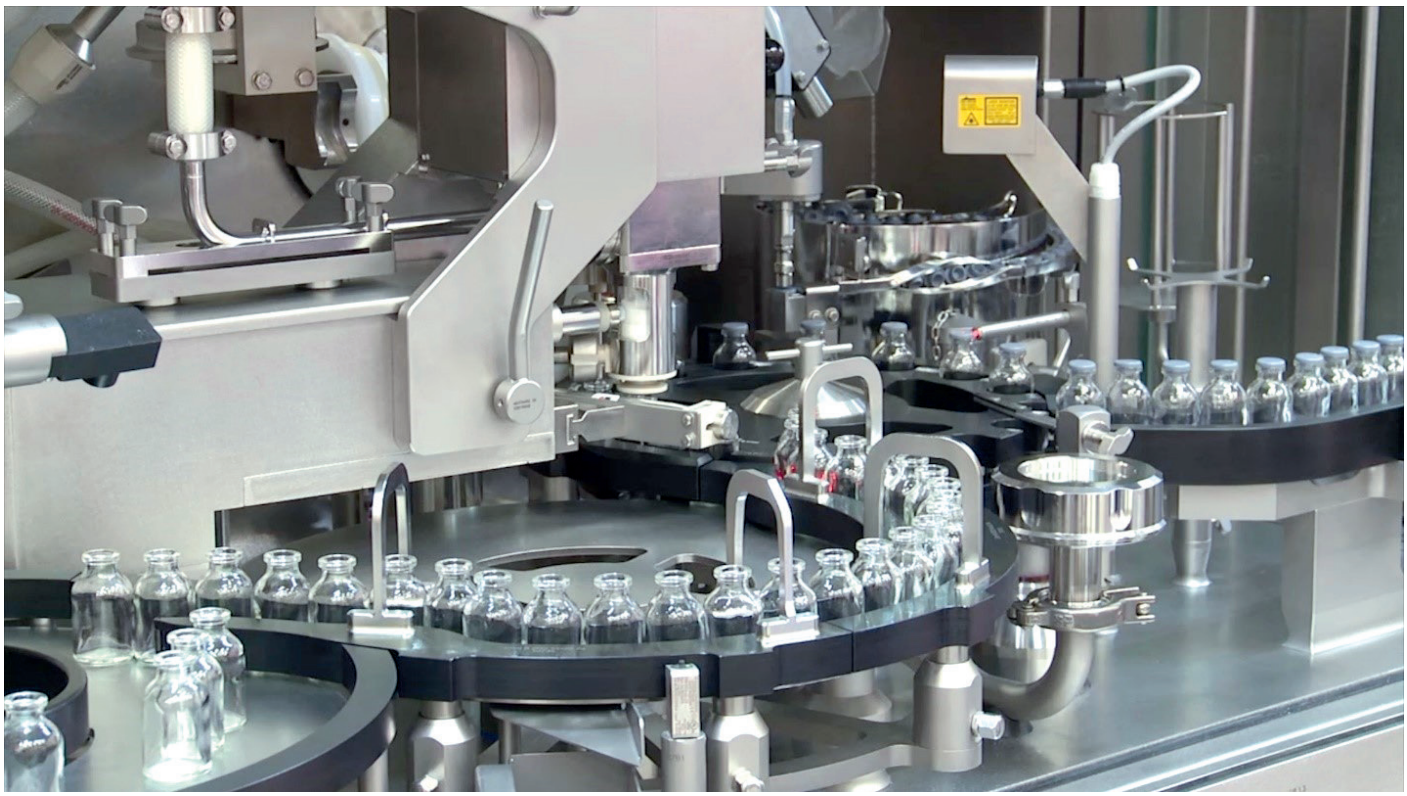

Figure 5: A modular, automated aseptic line at Evonik's Birmingham (AL, US) site for the filling of powders, liquids or suspensions into vials.

Evonik is a global CDMO for advanced drug delivery. For complex parenteral drug products, the company provides a broad portfolio of functional excipients and a range of CDMO and aseptic filling services compatible with more than six drug delivery technology platforms. In addition to LNPs, these platforms include polymeric nanoparticles, nanoparticles, micelles, implants and *in situ* forming. For LNP-based drug products, Evonik has more than 25 years of industry experience through its acquisition and integration of the Canadian CDMO Transferra NanoSciences (previously Northern Lipids). Approximately 50% of all LNP-based drug products approved to-date have received the support of either Evonik or Transferra.

Evonik has developed hundreds of LNP-based formulations for gene and cell-based therapies as well as other nanomedicines with a broad, global base of pharmaceutical and biotech companies. A range of CDMO services are available to support customer projects from drug discovery and preclinical studies through to the large-scale GMP production and aseptic filling of the final drug product. The company provides its LIPEX® extruders ranging from benchtop to commercial production scale, and also has extensive in-house manufacturing capabilities as well as other industry relationships for micromixing (Figure 5).

Since the acquisition of Transferra, Evonik has transformed its Vancouver (Canada) facility into a centre of excellence for drug products that require liposomal and nanoparticle technologies for delivery. These investments have effectively doubled the size of the company's Vancouver site, and considerably expanded manufacturing and formulation development capabilities that are available to support new customer projects. In parallel, Evonik has begun to harmonise the equipment and processes at both its Vancouver site and its late stage/commercial manufacturing site for complex parenteral drug products in Birmingham, AL, US. Through these and other investments, Evonik is now positioned to assist pharmaceutical customers in the development of liposomal-based parenteral drug products to support their entry into human clinical trials and their scale-up for commercial use.

ABOUT THE COMPANY

Evonik is one of the world's leading CDMOs for advanced drug delivery. For oral and parenteral drug products, Evonik provides customers with a broad portfolio of functional excipients, drug delivery technologies, formulation development, process development and cGMP manufacturing services. As a CDMO for complex parenterals, Evonik has more than three decades of expertise with drug delivery technologies including polymeric microparticles and nanoparticles, lipid nanoparticles, drug-loaded implants, micelles and *in situ* forming. Evonik is also a leader for process technologies including micro-encapsulation, precise hot-melt extrusion and liposomal extruders. Additional services include the contract manufacturing of APIs and intermediates, and the supply of amino acids plus other pharmaceutical and cell culture ingredients.

ABOUT THE AUTHOR

Stephen Allan is a healthcare communication specialist with more than 20 years of expertise across global drug delivery, medical device and nutraceutical markets. After graduating in journalism, he has co-ordinated communication activities for Australian, US and European-based companies. Based in Germany since 2017, Mr Allan supports global communication activities for the Evonik Health Care business line.

BATTELLE

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CHALLENGES AND CONSIDERATIONS IN CUSTOMISING PLATFORM DEVICES

How do you choose the best delivery system for your drug? Doug Boyd, Manager, Medical Devices at Battelle, explores the pros and cons of a cost-effective, off-the-shelf platform versus a custom drug delivery device. He also discusses the challenges and considerations of customising an existing platform device.

A well-considered drug delivery system can maximise the effectiveness of innovative small molecule and biologic therapies. But how do you choose the best system for your drug? Do you choose a cost-effective, off-the-shelf platform or invest in developing a custom drug delivery device? There are pros and cons for each option – and there is also a third path to consider. Adapting an existing platform device with a few custom attributes tailored to your molecule can offer the best of both worlds.

Adapting an existing device can enable faster timelines, lower costs and potentially smoother regulatory approval compared with custom device development, while still providing key attributes needed to optimise drug delivery and maximise the market potential for a drug.

> "Adaptation of an existing platform device is a practical and effective solution for drug developers who do not want to invest the time and money to develop a completely custom device but need specific attributes not available in an off-the-shelf model."

With many existing drug delivery platforms to choose from, chances are good that drug developers can find one that gets them 80% of the way to the optimal device. But how do you solve the technical challenges required to address the remaining 20%? For successful adaptation of a platform drug delivery device, you need a development partner who understands how to "innovate inside the box" to optimise outcomes and minimise risks.

WHAT IS INNOVATING INSIDE THE BOX?

Drug developers have three routes to matching a drug with a delivery device, each with its own trade-offs between cost and time to market and the degree of customisation desired:

- They can adopt an existing off-the-shelf device to use as is with their molecule
- They can create a brand-new, completely custom device from scratch
- They can innovate inside the box and adapt an existing platform device with custom attributes to meet unique drug, user and market requirements.

Adaptation of an existing platform device is a practical and effective solution for drug developers who do not want to invest the time and money to develop a completely custom device but need specific attributes not available in an off-the-shelf model.

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HOW TO 'INNOVATE INSIDE THE BOX'

When adapting an existing platform device, device engineers must:

- Work within the constraints and tolerances of the original platform device
- Innovate within those constraints to find the optimised delivery solution for the given drug formulation, user requirements and business needs.

First, we must prioritise and optimise the drivers for customisation. What attributes are essential for safe and effective delivery of the drug? These might include adaptations to account for the physics of the drug's formulation (e.g. high viscosity), the needs of the administration route or end-user needs uncovered through prior research. What attributes are desirable but non-essential? These might include things like a compact device or a particular form factor, which may be desired by end users but will not make a critical difference in drug administration or market opportunity. These drivers need to be weighed and balanced against each other – especially if some turn out to be mutually exclusive.

The next step is finding the appropriate device for customisation. Which platform is closest to meeting the requirements? Which platform offers the most potential for customisation in ways that would meet the essential requirements? How would each platform need to be changed to meet the desired characteristics?

Then, we must evaluate the impact of proposed changes to the device. Any proposed change must address two problems: the one you are trying to fix, and the one you create by introducing the change. For example, changing the physics of the device – such as making the spring stronger to accommodate a higher-viscosity drug – may put too much stress on other device components, leading to earlier failure or shelf-life issues. Additional changes may need to be made to compensate, such as choosing a stronger material for the housing or a different type of snap-fit or adhesive for joined parts. If the negative impact outweighs the benefit, you may need to look for alternative solutions.

Finally, the proposed solutions must be weighed and balanced. How well do they meet the requirements? What are the negative impacts? What are the costs, timelines and risks associated with each solution? There may be a tipping point where it becomes apparent that full customisation is a better option.

	Adopt (Use an existing box)	Adapt (Innovate inside the box)	Create (Build a new box)
Pros	• Likely lowest cost (a fraction of the cost of custom development) • Near immediate availability to speed time to market • Significant risk reduction (already tested and approved)	• Faster and less expensive than custom development with similar advantages • Reduces risks and timelines by starting with an approved platform • Enables platform device to meet specific requirements based on drug characteristics and patient population needs	• Addresses specific needs of patient population and unique drug characteristics • Creates a recognisable brand or unique market differentiator
Cons	• Not optimised for specific drug characteristics and target population • Does not deliver a differentiated market advantage	• More expensive than adopting an off-the-shelf device • Degree of customisation possible can be limited	• Higher development costs • Longer development timelines • Regulatory hurdles and risks
Best for	• Drug formulations with standard viscosity, dosage, delivery rates and administration routes (e.g. subcutaneous) • Patient populations without special needs • Markets where cost competitiveness is critical • Situations where taking the shortest path to market is essential	• Situations with modest formulation and special patient population needs, such as: – Formulation that needs slightly higher delivery force – Alternate dosing regimens or other preparation considerations – Minor grip or use enhancements – Need for competitive differentiation via user experience	• Situations with significant drug formulation and special patient population needs, such as: – Unique physical characteristics (e.g. high viscosity/high delivery rate) – Dexterity or cognitive needs, special connectivity, etc. • Treatments, or pipelines full of treatments, leveraging similar formulation/ delivery strategies with large market opportunities where product differentiation will deliver a substantial benefit

Table 1: Pros and cons of the adopt, adapt or create trade-offs.

MAKING THE CHOICE: ADOPT, ADAPT OR CREATE

What are the pros and cons of the "adopt, adapt or create" trade-offs (Table 1)? How do you reach the optimised balance of feature sets and time/cost to market (Figure 1)?

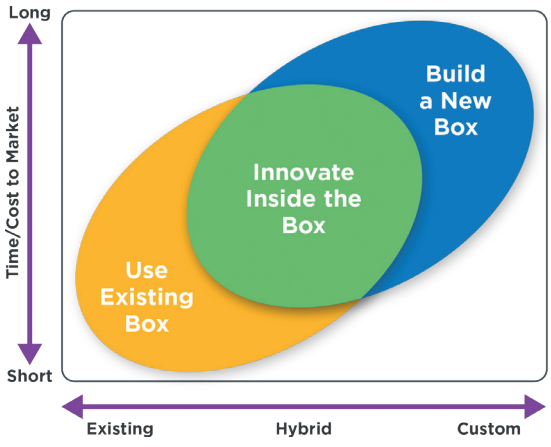

Figure 1: Innovating inside the box – time/cost versus customisation trade-offs.

DRIVERS FOR CUSTOMISATION OR ADAPTATION OF DRUG DELIVERY DEVICES

There are many reasons why an off-the-shelf drug delivery platform may not be right for a given therapy. These can be broadly grouped into three areas (Table 2):

- **Drug formulation considerations** – the physics, dosage, injection rate, administration route and storage requirements of the molecule are key drivers for customisation. For example, a device may need to be adapted with a stronger spring to accommodate a very high-viscosity drug formulation.
- **User requirements** – special populations such as children or patients with cognitive or dexterity challenges may require adaptation of a device to make the device easier or less confusing to use.
- **Business drivers** – adaptation may also be used to deliver a business advantage, such as providing a clear market differentiator. The decision to adapt or customise may also be driven by market size and pipeline considerations; the larger the market opportunity, the more it makes sense to invest in adaptation or customisation.

The decision to customise or adapt comes down to weighing the various drivers. Imagine this as a seesaw, with unique and special needs stacked on the right and ordinary, off-the-shelf attributes on the left. A large number of significant uniqueness drivers – e.g. high viscosity, non-standard administration route, special storage requirements, a special patient population and a large market opportunity – will tip the balance towards a full custom development as the best solution. Likewise, having very few or no uniqueness drivers will tip the balance towards a fully leveraged platform device. Often, however, the blend of common and custom features desired leaves the balance more even, leading to a best choice of adapting an existing design (Figure 2).

> "There are many reasons why an off-the-shelf drug delivery platform may not be right for a given therapy."

Customisation drivers		
Drug formulation	User requirements	Business drivers
• High viscosity (greater than 15 cP) and/or delivery volume (greater than 2 mL) • Non-standard delivery speed • Non-standard administration route (e.g. intramuscular, oral, intrathecal, intradermal, ocular) • Special storage requirements (e.g. refrigeration) • Requires reconstitution prior to delivery • Frequency/complexity of dosing regimen	• End-user characteristics (child versus adult, patient versus caregiver, etc.) • Physical and cognitive abilities of end users • Lifestyle considerations • Sustainability/disposal requirements • Visibility requirements for drug or delivery mechanism • Storage/portability requirements • Weight/ergonomics • Value of connectivity/ apps for condition management	• Time-to-market requirements • Importance of device to branding/market differentiation • Patient preference • Pipeline considerations (similarity to launched or pipeline molecules) • Market size/opportunity

Table 2: Drivers for customisation of drug delivery devices.

Real-World Example: A Low-Tech, Low-Cost Solution to Reduce Patient Anxiety

- An autoinjector needed a window to allow patients to see the liquid inside, as per regulatory requirements. Adding the window also unmasked the needle, which caused increased anxiety and lower levels of acceptance for some patients.
- Adding an opaque façade over the tip re-obscured the needle while still allowing the liquid to be seen clearly through the window.
- Adding the façade was a low-cost solution with no negative downstream effects. The façade did not require a redesign of the device and only required a minor change to the manufacturing process. Obscuring the needle improved patient acceptance of the device.

Real-World Example: An Alternative Solution to Reduce the Negative Impacts of Change

- An autoinjector needed a spring with more force to push a more viscous drug. Using a larger spring would have required a complete redesign of the device, with a larger barrel and other significant engineering changes.
- A double spring with right-hand and left-hand springs coiled together provided double the push in approximately the same diameter.
- The existing device could be easily retrofitted with the new double spring. This solution avoided major engineering and manufacturing process changes and got the new molecule to market faster.

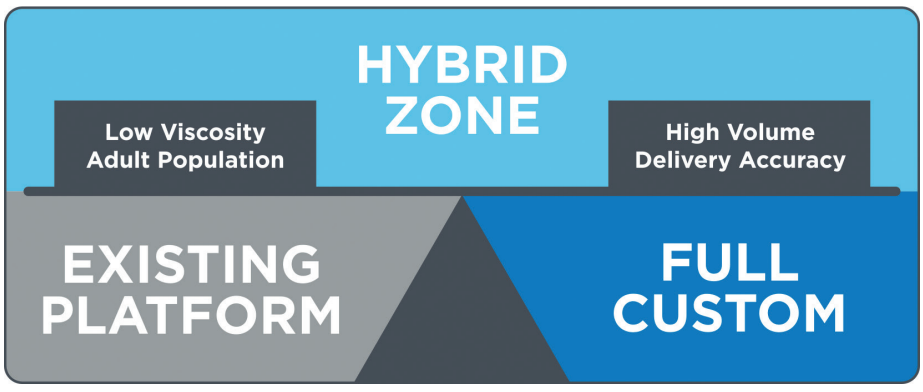

Figure 2: Weighing the drivers to determine customisation or adaptation.

FINDING THE RIGHT PARTNER FOR PLATFORM CUSTOMISATION

When customising a platform device, you need a partner who understands all the parameters and constraints, including the engineering and physics of the device, downstream effects, user impacts and business requirements. The right partner will be able to:

- Help you pick out an appropriate platform, suggest the changes required to meet essential and desired device characteristics, predict the potential negative impacts of each change and provide mitigation solutions.
- Find solutions that will be feasible in the real world and minimise potential downstream effects on supply chains and manufacturing processes.
- Understand how proposed changes impact the usability of the device and provide solutions that work for the target patient population.
- Help you perform a cost/benefit analysis for adaptation versus creation of a custom drug delivery device so you can make an informed decision based on business, market and patient needs.
- Help you understand and reduce risks, including safety, performance and market and regulatory risks.

Battelle has the right combination of expertise and experience to innovate inside or outside the box. We can help you select the right platform for your molecule, adapt a platform to your needs or develop a fully customised drug delivery device from scratch. We bring you decades of expertise in:

- **Device design** – our 25+ years of experience in custom device design, combined with our continual evaluation of dozens of drug delivery platforms each year for human factors evaluations or technical due diligence, has informed our team of designers so they can optimise the balance between user needs and commercialisation needs.
- **Device engineering** – we have decades of experience in all facets of drug delivery device design and engineering, from materials selection to Internet of Things connectivity. Our team brings specific expertise in state-of-art injection, patch pump and inhalation technologies, and is behind three of the most successful drug delivery platforms of the last decade.
- **Human factors evaluations** – with the patient always in mind, our team applies human-centric design principles and has deep experience in human factors studies and device usability. We can help you understand how proposed changes may impact the usability and acceptance of your drug delivery device and can develop solutions that better meet the needs of your end users.
- **Regulatory experience** – we understand the range of applicable regulatory processes (e.g. BLA, NDA, 505(b)(2), etc.) and can predict how proposed changes to a platform device may impact approval. We will help you make the right decisions and gather the right information to reduce regulatory risk and ensure a smooth submission process.

Our experience and multidisciplinary approach give us the ability to foresee the positive and negative impacts of a proposed change – not just from a device engineering perspective but also from the regulatory, commercial and market perspectives. The Battelle team can be relied upon to provide unbiased, expert advice to help you maximise your opportunities and reduce the risks, costs and timelines for device development.

ABOUT THE COMPANY

Battelle is one of the world's largest, independent, non-profit research and development organisations. It is a US$8.2 billion (£6.3 billion) enterprise with a mission as relevant today as it was when it opened its doors more than 90 years ago – to translate scientific discovery and technology advances into societal benefits. Headquartered in Columbus (OH, US), Battelle focuses its contract research efforts on three main areas: health, national security and environment.

ABOUT THE AUTHOR

Doug Boyd has dedicated his career to helping people by making new medical technologies a reality. He leads Battelle's multidisciplinary medical device and health analytics business, encompassing experts in programme management, systems engineering, electrical, mechanical and software engineering, human centric design, advanced data science and quality/regulatory compliance. Mr Boyd holds 22 patents and has been involved in the development of dozens of complex medical devices for commercial and US government clients, including surgical equipment and tools, *in vitro* diagnostic systems, self-administered drug delivery devices and in-hospital drug administration systems.

We inject innovation, collaboration and precision into your drug discovery process.

battelle.org/drug-delivery

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It can be done

MEETING DEMAND BY BRINGING MANUFACTURING IN-HOUSE

In this article, Bentsi Algazi, Vice-President of Operations, and Anna Kalika-Rodin, Quality Manager, both of Sorrel Medical, discuss the process of developing and implementing in-house production facilities at Sorrel Medical, including cleanroom facilities. The authors discuss the regulatory requirements involved, practical considerations of the design and construction, and the benefits the establishment of in-house facilities confers to Sorrel and its pharmaceutical partners.

Growing recognition of the need for patient-centric drug delivery devices, combined with the increasing prevalence of biologics and a general trend towards home care and self-administration, has led to greater demand for disposable and easy-to-use wearable injectors. As such, pharmaceutical manufacturers are increasingly investigating wearable drug delivery solutions as an option for launching new products to market, as well as for lifecycle management of combination products already in circulation. Consequently, device manufacturers and technology vendors must align themselves with pharma's evolving development needs – to deliver devices that meet pipeline expectations, while ensuring all the quality controls and necessary standards are maintained.

"Throughout the construction and implementation process, consistent monitoring, evaluation, and revaluation was required to ensure that all cleanroom standards were being upheld."

With an understanding of the direction in which the industry is moving, Sorrel has established its own independent manufacturing and cleanroom facilities to accommodate scalable production of wearable drug delivery devices (Figure 1). As demand from multiple customers increases, it is essential that Sorrel's manufacturing capabilities can scale-up accordingly, while still maintaining a level of quality that meets the highest requirements throughout the production process. Customisation and adaptable manufacturing capabilities allow for Sorrel to manufacture devices according to customer requirements, either in-house or outsourced to third-party providers.

THE DECISION TO IMPLEMENT IN-HOUSE MANUFACTURING

Looking to expedite the transition from initial design and development, with low-

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Figure 1: Sorrel has established its own in-house cleanroom facilities as part of its development of scalable in-house manufacturing capabilities for its wearable injector platform device.

volume manufacturing, to medium- and high-capacity production of wearable drug delivery devices, in line with the needs of global pharma, Sorrel began the process of establishing a dedicated in-house manufacturing facility. The cleanroom (an integral component for the manufacturing process, scientific research, and quality control) required careful consideration with respect to both the design phase and the actual use of the facility once established.

The primary motive for establishing facilities for in-house manufacturing was to ensure that Sorrel meets manufacturing demands with the proper level of quality for future products, whether developed for R&D purposes, clinical studies, or ongoing commercial device production. In conjunction with establishing in-house cleanroom operations, Sorrel engaged leading contract manufacturing organisations (CMOs). The option of utilising a third-party CMO can be examined, either in parallel or in addition to commercial in-house manufacturing, on a partner-by-partner basis.

The International Organization for Standardization (ISO) standards ISO 14644/14698 (Table 1) and EudraLex GMP Annex 1 served as guiding requirements for the cleanroom setup and operation, as well as for microbial monitoring during manufacturing. Therefore, beginning with the design phase, careful consideration was necessary to determine:

- How the cleanroom would be used
- Where the cleanroom would be located
- The permitted particle concentration
- The manufacturing process requirements
- The cost.

Sorrel sourced and continually engaged with cleanroom consultants in order to review the process and ensure complete compliance with all required standards. Concurrently, it was necessary to liaise with pharmaceutical partners to establish

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
1	*10*[b]	[d]	[d]	[d]	[d]	[e]
2	100	*24*[b]	*10*[b]	[d]	[d]	[e]
3	1,000	237	102	*35*[b]	[d]	[e]
4	10,000	2,370	1,020	35	*83*[b]	[e]
5	100,000	23,700	10,200	3,520	832	[d, e, f]
6	1,000,000	237,000	102,000	35,200	8,320	293
7	[c]	[c]	[c]	352,000	83,200	2,930
8	[c]	[c]	[c]	3,520,000	832,000	29,300
9[g]	[c]	[c]	[c]	35,200,000	8,320,000	293,000

Table 1: ISO 14644-1:2015 cleanliness requirements.

a All concentrations in the tale are cumulative, e.g. for ISO Class 5, the 10,200 particles shown at 0.3 µm include all particles equal to and greater than the size.
b These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied.
c Concentration limits are not applicable in this region of the table due to very high particle concentration.
d Sampling and statistical limitations for particles in low concentrations make classification inappropriate.
e Sample collection limitations for both particles in low concentrations and size greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.
f In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size.
g This class is only applicable for the in-operation state.

their specific development expectations and pipeline needs. From there, Sorrel began a process of constant knowledge acquisition, application, implementation, and evaluation, to build the facilities that would best serve the needs of both Sorrel and its strategic partners. The result was an ISO-7 level (Grade C, per EudraLex GMP Annex 1) cleanroom integrated within the new manufacturing facility, which also includes a front warehouse, Incoming Quality Control (IQC) lab, washing room, and ISO-8 (Grade D)-rated gowning room.

THE IMPLEMENTATION CYCLE

The ISO provides the guidelines for cleanliness requirements, and according to that the cleanroom classification is set. Throughout the construction and implementation process, consistent monitoring, evaluation, and revaluation was required to ensure that all cleanroom requirements were being upheld. The extensive testing – including smoke tests, air uniformity, recovery tests, microbial counting, and particle counting – were performed to ensure compliance with the highest standards required for implementation. The new facility will exclusively manufacture Sorrel's own fully disposable wearable injectors (Figure 2) for design and development activities, feasibility studies, clinical studies, and commercialised products.

> "Making the transition from outsourcing manufacturing to third-party providers to establishing in-house production for clinical trials and commercial output allows for greater control of production and improves device manufacturing processes from both a regulatory and quality perspective."

The decision to include the 80 m² cleanroom within the facility enables Sorrel to begin production with a capacity of hundreds of thousands of units per year, with the flexibility to further increase output as necessity dictates. As an ISO-7 class environment, the production cleanroom is specifically intended to reduce particulate and microbial contamination in accordance with ISO 14664-1:2015 and EU GMP Annex 1 requirements, as well as controlling other environmental parameters, such as temperature, humidity and pressure.

One of Sorrel's top priorities in establishing the facility was to focus on the future growth of the company. The decision was therefore made to invest in and build a facility that would be able to support the company's rising production forecasts. In due time, as more sections of the assembly line are brought online and existing features are changed or upgraded, regulations and standards are to be monitored and internal processes updated accordingly. Thus, implementation is a constant cycle of learning, appraisal, and adjustment. Sorrel's Quality Management System (QMS) certification, granted by a notified body, ensures annual inspection of the implementation process, thus ensuring compliance with up to date cleanroom regulations and company quality policies.

COMPLIANCE IS KEY

Once a cleanroom is up and running, it needs to be meticulously maintained to guarantee its continued integrity. Great care must be taken to minimise contamination risks, including restricting access to a select number of specially trained employees, as well as carrying out constant cleaning, maintenance, and monitoring, with frequent inspection of particulate and microbial matters. This requires intense quality control measures to be implemented and adhered to on an ongoing basis. Any non-conformance or misalignment with the monitoring of the cleanroom environment must be mitigated immediately according to established processes, protocols and corrective actions.

As Sorrel's devices are intended for direct, self-administration of medication by patients, the manufacturing environment requires airborne particle control to mitigate any risk of contamination during the assembly process. All products must therefore undergo further sterilisation via ethylene oxide (EtO) by a certified supplier, after being packed in the cleanroom in Tyvek and blister packages, specially designed for each product (Figure 3).

Making the transition from outsourcing manufacturing to third-party providers (primarily for R&D purposes) to establishing in-house production for clinical

Figure 2: The Sorrel Medical wearable injector platform.

Figure 3: A Sorrel Medical device and its blister pack.

"Establishing and maintaining one's own manufacturing facility requires significant commitment and demands that the manufacturer is invested in the process on a daily basis. While the challenges involved in this are considerable, the benefits are tangible."

trials and commercial output allows for greater control of production and improves device manufacturing processes from both a regulatory and quality perspective. With respect to operational and quality considerations, the facility must be of a suitable size, construction, and setting to ensure that cleaning, maintenance, and operations can be performed as stipulated. Additionally, the facility must have adequate space and operational flow design to prevent potential errors and cross-contaminations; surfaces that are easy to clean; and the capability to control temperature, pressure, and humidity. Air within the room is kept at a positive pressure and is HEPA-filtered, environmental conditions are constantly monitored, and all equipment, as well as the cleanroom itself, is regularly cleaned and disinfected to maintain the ISO Class 7 requirements.

All employees need to undergo specific training to understand the importance of behaviour and proper disinfection in a controlled environment. The operation and maintenance of the cleanroom has necessitated numerous additions to Sorrel's QMS, in the form of procedures, dedicated work instructions and additional controlled processes, to comply with all the standards and requirements for cleanroom certification. Final accreditations – including Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) – were required to ensure that all components are correctly installed, that the installation meets its design requirements and specifications, and that it operates as intended.

CHALLENGES AND BENEFITS

Establishing and maintaining one's own manufacturing facility requires significant commitment and demands that the manufacturer is invested in the process on a daily basis. While the challenges involved in this are considerable, the benefits are tangible.

Ensuring that production remains within close proximity to R&D and operations means that all associated activities can be performed in-house. This grants Sorrel considerably more control over processes, as well as facilitating quality assurance, which is required on a continual basis. Additionally, as a development project nears the design transfer phase (in which the R&D engineers essentially pass the responsibility of the device over to the operations and manufacturing teams), the proximity between the R&D offices, quality team, and manufacturing site proves to be imperative for quick and efficient resolution of any issues that may arise.

Another key benefit that in-house manufacturing provides is a considerable saving of time and resources. In-house manufacturing allows for frequent audits and inspections of the cleanroom to be conducted internally, rather than Sorrel having to audit external suppliers. Additionally, the opportunity to directly manage all manufacturing processes independently eliminates the reliance on, and waiting time for, other contractors, enabling a much faster turnaround for initiating full-scale production.

Finally, having a dedicated and independent facility enables it to flexibly cater to Sorrel's specific needs, granting Sorrel autonomy to run the production line and develop customised tools and fixtures for production automation to best serve its clients.

The same goes for capacity – if so desired, Sorrel can potentially extend manufacturing to round-the-clock production. The fact that all technicians and lab personnel involved in production are now dedicated Sorrel employees, with a vested interest in the company's success, engenders greater commitment and professionalism that further enhances quality and productivity. Not only that, but in an industry where partnerships between device manufacturers and pharmaceutical companies are often confidential by nature until commercial launch, having these activities take place within the company's premises ensures confidentiality is maintained.

INCREASING CAPACITY THROUGH AUTOMATION

Increasing the capacity of a production line is dependent on numerous contingencies, but Sorrel will continuously improve its capabilities with time as production is increasingly automated. High capacity, already achieved through the introduction of both semi- and fully automated tools to assembly lines on a consistent basis, positively impacts the quality and consistency of the entire manufacturing

process. This has already resulted in Sorrel's increased production of higher quality products.

As the company continues to expand, increased manufacturing capabilities will enable Sorrel to support global pharmaceutical and biotechnology partners in bringing the highest quality of wearable drug delivery solutions to patients.

ABOUT THE COMPANY

Sorrel Medical is a medical device development and manufacturing company focused on prefilled wearable, on-body injectors. Its technology platform, based on a robust patent estate, is prefilled and preloaded, and is intended for the subcutaneous delivery of biologics, biosimilars and small molecules (doses of 1–25 mL). The platform is suited for multiple configurations, molecules, and indications, and is digitally integrated with Bluetooth and NFC connectivity.

Sorrel is one of three privately held companies operating under the Eitan Group, all in the field of drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical. Q Core Medical develops and manufactures the Sapphire infusion system, on the market in both hospital and homecare environments. Avoset Health is developing a connected homecare infusion pump, available for pharmaceutical companies in a dedicated application configuration.

The joint experience shared amongst the Eitan Group's three companies includes development, commercialisation and manufacturing of drug delivery products across the continuum of care; multiple US FDA approvals; market presence in over 20 countries; and an R&D team with experience in parenteral drug delivery, accuracy, flow control, human factors and cybersecurity.

ABOUT THE AUTHORS

Bentsi Algazi is the Vice-President of Operations at Sorrel Medical. As such, Mr Algazi oversees all of Sorrel's supply chain, engineering, production, and vendor management activities. Prior to Sorrel, he was Micro-Infusion R&D Site Manager at West Pharmaceutical Services, leading the team responsible for bringing the company's SmartDose® wearable injector to commercialisation. Before joining West, he served as COO at PowerPaper, a developer of micro-electric solutions for cosmetic & RFID applications. He holds an MBA and a BSc in Physics and Mathematics from the Hebrew University of Jerusalem.

Anna Kalika-Rodin is Quality Manager at Sorrel Medical. As such, she leads the company's quality activities and ensures Sorrel's QMS complies with all the latest standards and regulations. Ms Kalika-Rodin and her team are responsible for the company's QMS, documentation, audits, and more. Prior to Sorrel, she worked as a Quality Engineering Team Lead at Q Core Medical, a manufacturer of drug delivery devices. She holds a BSc in Quality Engineering from the Technion-Israel Institute of Technology.

DOSAGE FORMS ROUNDTABLE: **JEREMY DRUMMOND**, MEDPHARM; **STEPHEN RODE**, LONZA; AND **TORKEL GREN**, RECIPHARM

Jeremy Drummond joined MedPharm in February 2017. Dr Drummond has spent over 20 years leading the commercial supply of product and services to pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships and marketing MedPharm to its global customer base. He started his career as a technical formulator and has a PhD in organic chemistry from the University of Cambridge, UK.

Stephen Rode is Manager of Business Development for Lonza's Capsules and Health Ingredients group. He received his BS in Agronomy from Pennsylvania State University, US, and a GBA in Executive Management from The Wharton School at the University of Pennsylvania in 1988. With more than 31 years of industry experience, Mr Rode has worked with many top pharmaceutical and consumer healthcare companies. In addition to sales and business development responsibilities, he has actively participated on various internal capsule development teams.

Torkel Gren, Science & Technology Officer, Recipharm, holds degrees in Pharmacy and Business Administration and a PhD in Pharmaceutics (Uppsala University, Sweden). Dr Gren has worked in the pharmaceutical industry since 1988 and has held a number of scientist and manager positions in Europe and the US. He was lead formulator and co-inventor of Detrol OD/Detrusitol SR. Dr Gren is a member of the board of the Swedish Pharmaceutical Society.

In this roundtable discussion, Jeremy Drummond, Stephen Rode and Torkel Gren talk with ONdrugDelivery about trends with different drug dosage forms for different routes of administration, the rise of patient centricity including the shift from the blockbuster model to more tailored products, and how successful industrialisation is dependent on considering factors such as manufacturability early in the development process.

Q In your opinion, what have been the biggest trends that have impacted drug dosage form development and industrialisation over the past 5–10 years and why?

JD The continual rise of biologics has brought with it the creation of new solutions to challenges surrounding these complex entities, in terms of packaging, analysis, delivery and stability. Standing at the forefront of these solutions, MedPharm has demonstrated that some biologics, in this case aptamers, can penetrate skin and still be active despite their large molecular weight (20k Daltons). Through this research our experts have challenged current theories on skin penetration of large-molecular-weight drugs, offering hope for the discovery of new treatments for difficult-to-treat dermatological diseases.

SR Although there have been many development trends in drug delivery recently, one route that is likely to stimulate innovation for years is oral solid dose (OSD) administration. Most of the small-molecule drugs in development right now are being designed for oral routes. Regulators have made a huge impact by creating new, more efficient routes for drug development to help medications reach patients. These drugs are being designed from the beginning to have solid chemistries because oral administration is increasingly recognised as key to supporting patient centricity. Regarding patient preference, dose control and compliance, capsules offer developers proven capabilities with their new formulations. Lonza's Capsugel® business has been out in front of capsule development for decades, and continuous innovation across our product lines is directly serving a wide range of developer and patient needs.

TG Despite the steep increase in new biopharmaceutical products, small-molecule OSD products are still in high demand because of the opportunity they present to extend product lifecycles and leverage growth potential. The ideal dosage form should have broad applicability and that is one reason why tablets and capsules are still on-trend. Using tablets or capsules you can achieve many different release profiles, including immediate, prolonged and delayed release, orally disintegrating tablets and fixed-dose combinations. Consequently, there remains a lot of opportunity for companies across the OSD market.

One of the biggest trends remains developing novel, improved products based

on established APIs. This is not surprising as substantial benefits can be realised, including reduced costs and shortened development timelines, as well as exploring new administration routes to improve compliance.

Another big trend is the increasing demand for drugs that can be locally administered, for instance by inhalation or topical administration. Local administration presents a solution to deliver sufficient levels of drug to a target organ while minimising systemic exposure and side effects. In addition, there is mounting interest in more specialised local administration routes, including ophthalmic and vaginal administration and parenteral formulations for local delivery.

The increasing interest in parenteral products stems from the fact that most new biopharmaceutical products in development require administration by injection. While this is less convenient than oral administration, for many more serious indications, injectable dosage forms are acceptable when looking at the balance between benefit and inconvenience. The ongoing development of convenient and reliable autoinjectors is also contributing to this.

Q Have there been any significant innovations within the industry that have helped companies take advantage/stay on top of these dosage form trends and what trends do you see in the next decade?

JD Innovations around performance models have positively impacted dosage form development, particularly for products acting locally. Considerable advances have been around the use of *in vitro* models based on fresh human tissue to optimise the activity of drug formulations. Previously only used to measure permeation, these increasingly sophisticated models are now also used to monitor the activity of formulations. In the case of skin, MedPharm has techniques that allow us to keep fresh human skin viable for weeks, not days, in the laboratory – allowing us to conduct experiments over much longer timescales and de-risking any decision to enter clinical trials.

Over the next decade there are general trends which will impact dosage form development, such as more genome-specific products and more biologic-based activities. Undoubtedly the combination of dosage form delivery with technology, whether that be for monitoring the patient or in aiding the delivery, will be an important trend. It is an exciting time in the drug development industry and the COVID-19 pandemic has focused attention on the benefits that innovation can bring to ensuring patient centricity, as well as the value governments and populations place on health and wellbeing.

SR Therapeutic innovation is coming from all corners of OSD development and it seems that each individual capsule or tablet has to do more than ever before. For example, it has to deliver more API accurately, be smaller and easy to swallow, manage bioavailability and be capable of other integrated functions.

Innovation in larger molecules and biotech drugs has also meant increased focus on developing and delivering larger molecules such as proteins, peptides and monoclonal antibodies orally. Functional excipients have been made available to improve the stability and solubility of Class II biopharmaceutic compounds or to allow for targeted delivery – this has removed some potential barriers to oral bioavailability in these formulations.

Over the coming decade, we are sure to see developers packing more patient performance potential in each dose. The 505(B)(2) pathway, for example, provides for coming development of fixed-dose combinations, as well as other formulations to achieve better patient outcomes and dose compliance.

TG Manufacturers are increasingly employing various lifecycle management patent strategies, including the development of new drug formulations such as extended, controlled or rapid release formulations using APIs that are already on the market. Drug delivery innovation is becoming more important for pharmaceutical companies and this increases the need to partner with a CDMO during the early development stages with extensive knowledge of formulation development.

Over the years existing development approaches have been continually improved. This has made it easier to develop valuable dosage forms. Several technologies for modified release, for instance coated pellets, were also developed decades ago but are now easier to use as we have more experience in how to apply them. Another excellent example of innovation and improvement can be seen across the device area. While inhalation and injection devices have been around for decades, new devices are much easier to use.

Looking to the next decade, I think manufacturability will rise higher on the agenda. The cost of manufacturing and packaging could be a considerable part of the total cost of a drug and this is highly dependent on choices made during the development process. This is extremely important as it can impact profits but even more so as it may limit access to valuable new medicines. As such, dosage form development should always be done with large-scale manufacturing in mind.

Another promising development is in the area of precision medicine for smaller patient populations. Adapting conventional manufacturing technology and making it more flexible to allow for smaller batches may be very useful. Pellet technology and minitablets are examples of conventional manufacturing technology that allow a high degree of flexibility as it is easy to combine different pellets and/or minitablets to achieve combinations of multiple drugs in different doses and with different release rates.

Q What are the major challenges to overcome when trying to formulate a user-friendly formulation?

JD Incorporating patient centricity into a finished product must

"I think manufacturability will rise higher on the agenda. The cost of manufacturing and packaging could be a considerable part of the total cost of a drug and this is highly dependent on choices made during the development process. This is extremely important as it can impact profits but even more so as it may limit access to valuable new medicines. As such, dosage form development should always be done with large-scale manufacturing in mind."

begin in the formulation development and design processes, first by looking at the active ingredient. Understanding the key physical and chemical properties of the active are key considerations that cannot be left out as they often point the formulator to a particular dosage form – for example, first-pass metabolism issues which focus the formulator on dosage forms other than OSD.

Additional elements such as packaging of the formulation can play a crucial part in the patient centricity of any dosage form and must be considered in the overall product development. For routes of delivery that stray away from more traditional routes of oral or IV, the use of *in vitro* models, using fresh tissue such as whole eyes, cultured human nasal tissue or fresh skin, have been shown to de-risk the development of the optimal formulation for the patient for that particular API.

SR User friendliness aspects of development now centre on areas such as patient compliance, with manufacturers searching for the most patient-centric form that supports the therapeutic performance and safety of their formulation.

A key consideration when using capsules is the characteristics of the API. The size of a molecule can often make it more challenging to deliver a substance orally, for example with proteins. The solubility required will also require specific formulation approaches and dose, stability, odour and colour during formulation all need to be considered.

Sustainability is making inroads into delivery innovation. Manufacturers are now prioritising clean-label ingredients for their products. Provenance is vital and the pedigree of ingredients equally so, with the intent to provide vegan and/or all-natural forms where possible. Lonza's Capsugel® business recognised this trend early, introducing a high-quality clean-label HPMC capsules that not only serve cultural/market goals but also answer API compatibility objectives.

TG Different formulations present different user-friendliness challenges. Typically, oral formulations are very user friendly, however size, taste and odour of the product need to be considered. When it comes to inhalation, for most patients this is less natural than oral administration and it's important that the device is used correctly to ensure the right therapeutic effect. Developing a device and product combination which ensures that an unskilled patient receives the intended effect from their medication is the main challenge here.

> "Sustainability is making inroads into delivery innovation. Manufacturers are now prioritising clean label ingredients for their products. Provenance is vital and the pedigree of ingredients equally so."

There are many different factors at play when it comes to the user-friendliness of parenteral dosage forms. When administered by healthcare professionals the user is very skilled but prefilled syringes can still save valuable time. However, with patients increasingly self-administering parenteral products, devices that are simple to use, store and carry are crucial.

Q Has there been an increasing requirement to develop more user-friendly dosage forms, and if so, why?

JD The continuing rise in expectations of patients for dosage forms that suit their lifestyles as well as positively impacting their health, combined with an acknowledgment that meeting these criteria is directly linked to improved compliance, has driven the development of more user-friendly products. In severe cases patients will accommodate inconvenience, such as the use of injectables for severe psoriasis where topical applications are the convenient dosage form of choice when the same disease presents as mild or even less severe.

At MedPharm, end users' opinions and preferences are crucial from the start. These factors are incorporated into the product profile we establish with our clients from the very beginning. The expertise of the product developer allows them to manage any constraints whilst still delivering a dosage form that patients are happy to use. This knowledge is particularly important for smaller companies where it is not uncommon for some not to have thought about end users' preferences, particularly at the early stage of a project. As patient preferences can be revised and fully understood once a project has started, these new insights can be accounted for within the product and incorporated into any project goals.

SR Patient centricity has become incredibly influential and development pipelines are moving away from blockbuster drugs with one-size-fits-all dose forms to more personalised medicines.

This trend is manifesting itself in different ways, but the idea is essentially to make drugs perform optimally for more individual patients and this is sending pharma development in many new directions.

Market and patient access add to the objectives. For example, in emerging markets where nasal and pulmonary drug delivery is vital in combatting prominent respiratory conditions, capsule-based dry powder inhalants are preferred for their cost effectiveness and ease of use.

The ideal dose form must meet patient needs above all else. Increasingly, this is translating into specifying dose forms that decrease dosing frequency, control side effects and are easier to swallow – all attributes of capsules' continued appeal with consumers.

Pharma manufacturers are more connected to patients now than ever before through internal advocates, representative associations and discussion forums. Pharmaceutical developers are also collaborating with patients more effectively in trials, as well as after with post-market studies becoming a critical element of the process.

TG Compliance is a crucial factor when it comes to medication. If a medicine is not easy to take or tastes or smells unpleasant then patients are less likely to comply with their medication regime. This puts a great deal of importance on the development of more user-friendly dosage forms.

Assessing the user-friendliness of a dosage form is a diverse process as different patient

> "Remember that for hospital products the end users are doctors and nurses. When we talk about user-friendly drugs this needs to include how easy they are to administer in a clinical setting too."

groups will have different requirements. Focus groups with patients are vital to this end, using qualitative and quantitative methods to evaluate their preferences.

It is also important to remember that for hospital products the end users are doctors and nurses. When we talk about user-friendly drugs this needs to include how easy they are to administer in a clinical setting too.

Looking to the future, patients will likely demand more control over their own medication. Packages and devices that communicate with smartphones or other devices and make it possible to track dosing are likely to become more prominent.

Q What roles can an outsourcing partner play in optimising a drug dosage form and what benefits can be gained from outsourcing?

JD To ensure a patient-centric approach, pharmaceutical product developers are increasingly looking to expand away from traditional dosage forms. Due to their convenience and affordability, topical formulations for pharmaceutical delivery such as for eye, skin, airways or mucosal membranes have been increasing in popularity over recent years. The requirements for delivery for these specialist topical products mean working with an outsourcing partner has many benefits as the requirements for delivery are quite different from oral and IV routes of administration and require unique knowledge and experience that the majority of development companies do not have in-house.

In particular, the sophistication of *in vitro* models using human tissue, which MedPharm has pioneered, in the development of these products has greatly de-risked these development programmes. What you also get with a specialised contract developer like MedPharm is not only the 20 years of formulation development experience in a specific area but an in-depth understanding of what it takes to get a product to market whether it is a new chemical entity, a re-purposed drug for a new indication, an OTC product or a generic.

> "Although globally there is a lot of manufacturing capacity for solid dosage forms, much of this capacity was designed to suite the old "blockbuster" paradigm. As a result, many manufacturers are looking to work with CDMOs that can offer more flexible manufacturing capacity."

SR The dialogue is yielding a great deal of influence in drug development, but also driving the need for expert partners and suppliers to deliver the technologies and capabilities pharma needs to pursue the patient-centric aspects of their drug products.

Nevertheless, emerging development and therapeutic goals are introducing manufacturing complexity in new ways. For example, many new APIs are highly potent and many have complicated chemistries that make controlling and modifying release a critical aspect of therapeutic performance and dose compliance. Increasingly, those goals are being met with external partners.

TG Today, there is growing interest in more specialised products often with relatively low production volumes, as well as a continued interest in new products with improved properties based on existing APIs. Although globally there is a lot of manufacturing capacity for solid dosage forms, much of this capacity was designed to suite the old "blockbuster" paradigm. As a result, many manufacturers are looking to work with CDMOs that can offer more flexible manufacturing capacity.

Pharma sponsors rely on CDMOs to help them get new products on the market. Many customers have very innovative projects and the ability to solve different challenges and manage complexity when developing and scaling up an innovative product is vital. These customers need a partner in innovation. Access to more technology, expertise and competence for dosage form development, locally as well as globally, can be gained through partnering with a CDMO.

> "Developing the dosage form with manufacturability in mind can have many benefits. Working with an end-to-end CDMO can help to reduce complexity, timelines and ensure smoother progress of a drug to market."

CDMOs that offer both development and commercial manufacturing services can help guide their customers' molecules from concept to market. As discussed earlier, developing the dosage form with manufacturability in mind can have many benefits. Working with an end-to-end CDMO can help to reduce complexity, timelines and ensure smoother progress of a drug to market.

ABOUT THE COMPANIES

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

Lonza Capsules and Health Ingredients is a global capsule and equipment developer and manufacturer which designs and produces innovative products for a wide range of oral dosage forms across the pharmaceutical and consumer health and nutrition market. By combining science, engineering and expertise with innovation and flexibility, the company provides quality products to more than 4,000 customers in over 100 countries and can offer advice on how to achieve customised solutions that optimise formulations and align with project and consumer requirements.

Recipharm is a CDMO headquartered in Stockholm, Sweden with development and manufacturing facilities in France, Germany,

India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US. The company continues to grow and expand its offering for customers. Employing around 5,000 people, it is focused on supporting pharma companies with its full-service offering, taking products from early development through to commercial production. For more than 20 years, it has provided pharma expertise and managed complexity for its clients throughout the entire product lifecycle.

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ON drugDELIVERY

EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Sept 2020	Wearable Injectors	PASSED
Sept/Oct 2020	**NEW TOPIC – INAUGURAL ISSUE!** Drug Delivery & Enviromental Sustainability	Sep 14, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 24, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 8, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
Jan/Feb 2021	Prefilled Syringes & Injection Devices	Dec 17, 2020
Feb 2021	Novel Oral Delivery Systems	Jan 7, 2021
Mar 2021	Ophthalmic Drug Delivery	Feb 4, 2021
Apr 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
Jun 2021	Connecting Drug Delivery	May 6, 2021
Jul 2021	Novel Oral Delivery Systems	Jun 3, 2021
Aug 2021	Industrialising Drug Delivery	Jul 1, 2021

Stevanato Group

MEETING QUALITY DEMANDS THROUGH INTEGRATED PRODUCTS AND SERVICES

In this article, Lars Keinicke Hansen, Business Line Manager for Pharma Inspection and Packaging & Assembly; Chiara Mussoi, Product Manager for the Cartridge Platform; and Odra Pinato, PhD, Head of SG Lab Analytics Laboratory; all of Stevanato Group, describe how the streamlining of processes and harmonisation of products and services can better serve pharmaceutical companies. A case study highlights how a unique combination of expertise in automation and glass primary packaging benefited pharmaceutical giant Merck Serono in a recent project.

Combination products are being launched for an increasing range of therapies, including low-volume orphan drugs, high-volume pharmaceuticals and highly competitive biologics and biosimilars. However, very few pharma companies are equipped to handle these complex drug-device integration projects alone.

In a traditional supply model, a pharma company would source primary packaging from one vendor and the drug delivery device from another. Performance of these two separate constituents would be analysed and characterised by external laboratories. Automation specialists would fabricate assembly and testing equipment and yet another company would perform commercial production. This effort required a tremendous amount of co-ordination between the pharma company and various suppliers.

Organising information and materials, and sequencing the movement of both, can be an imposing task. The risks are high, as a single wrong step along the way could cripple a project. Delays to a drug launch can impact the lives of millions of patients around the world, as well as creating devastating financial consequences for the pharma company itself.

To minimise the risks and ease the burden on the pharma company, some suppliers have been expanding their offering

> "At the heart of any combination product is the primary packaging."

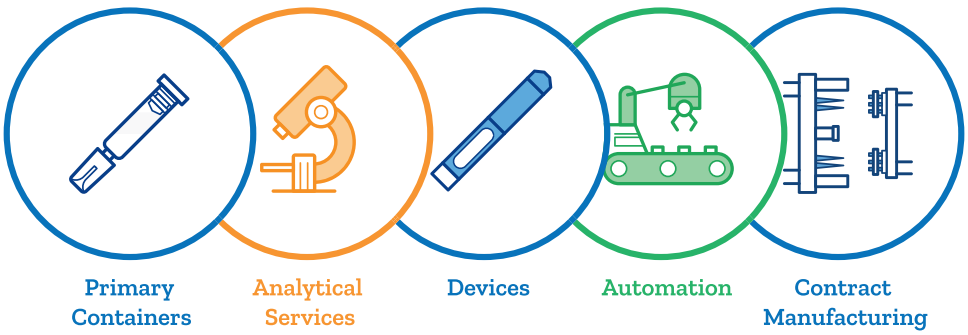

Figure 1: Working with integrated partners ensures smooth transitions of information and materials that streamline processes and harmonise products and services.

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by integrating one or more products or services to better serve pharma partners directly. The relationship between pharma companies and these suppliers has evolved into a collaborative partnership, with a joint desire and responsibility for project success.

HARMONISATION THROUGH INTEGRATION

As an integrated project partner, Stevanato Group supports pharma companies at all stages of the drug development journey through a comprehensive suite of products, technologies and services. Through continually expanding its capabilities, Stevanato Group can oversee a drug delivery device programme under a unified project management and quality system (Figure 1).

The experience gained from developing primary containers, integrating drug delivery devices and performing contract manufacturing services has enabled Stevanato Group to produce an intimate perspective of the critical path for any medical device project. This knowledge and experience are used to streamline processes and harmonise products and services. This includes expansion of the company's primary packaging offering through laboratory and analytical services, as well as streamlining its automation offering.

LABORATORY AND ANALYTICAL SERVICES

At the heart of any combination product is the primary packaging. This component plays a crucial role in protecting the drug product and enabling the delivery of medicine to patients. Stevanato Group is a leading provider of glass primary packaging for pharma and biotech companies, offering a range of high-quality EZ-fill syringes, vials, cartridges (ready-to-use containers) and bulk packaging options. These devices are relied upon for delivering diabetes treatment, emergency medication, vaccines and high-value biologic drugs throughout the world.

With its history of processing glass for pharma applications, Stevanato Group has amassed a large amount of technical data and experience in primary packaging and related components of the container closure system. This important industry resource can be accessed through the group's analytical and testing services.

Partnering with Stevanato Group provides access to an accredited laboratory with teams of scientific experts that perform research projects and studies to help customers understand the potential interactions between pharma products, their containers and delivery devices. Operating in compliance with ISO/IEC 17025 2018, these experts use the latest technologies and methods to perform a wide array of tests and assessments, including chemical analysis, surface characterisation, container interaction, and physical and mechanical performance, including drug delivery systems testing.

The output of these studies can help customers navigate critical decisions related to container selection, device compatibility and process improvements, bringing value to any stage of a drug delivery device programme. To increase access to these resources, Stevanato Group has expanded this offering through a recently announced Technology Excellence Centre in Boston, MA, US.

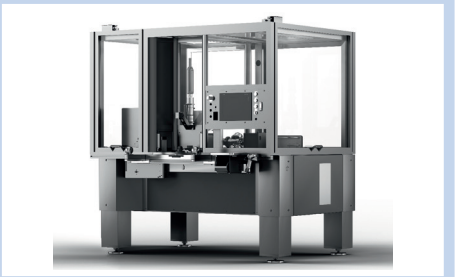
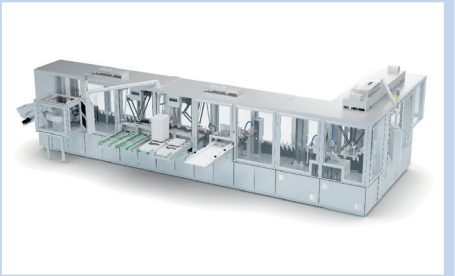
	Type	Description	Applications	Output Speed (parts per minute)	Flexibility
	**Benchtop or lab unit**	Low volume manual or semi-automatic assembly	Device & process development	1-6ppm	Fixtures are changeable to handle different products
	**Rotary**	Ideal for space saving assembly processes	Scale-up, clinical & low volume commercial production	6-40ppm	Machines can be linked together to reduce number of parts, processes and simplify reconfiguration
	**Linear (BasiQX XTV & XTH)**	Platforms based on linear transport system for complex assembly tasks	High-speed, large-scale commercial production	Up to 200ppm	Countless applications, accommodates different formats & future capacity needs at scale

Table 1: Stevanato Group has three customisable assembly platforms, bringing new levels of production flexibility and scalability for pharmaceutical partners.

SCALABLE AND FLEXIBLE AUTOMATION SOLUTIONS

In addition to this expansion, Stevanato Group has invested significant resources in how it delivers automated assembly solutions to clients. This streamlined approach centres on customisable platforms and modules that bring new levels of production flexibility and scalability for pharma partners, while reducing total cost of ownership.

Stevanato Group has applied its expertise and knowledge to develop three customisable platforms that form the foundation of its assembly solutions for autoinjector, pen injector, wearable and inhaler projects (Table 1).

Benchtop or laboratory units are available for device and process development purposes, including early proof of principle and assembly validation. Once the assembly process has been validated, it can be easily and rapidly scaled up to meet production demands, minimising risks through early debugging.

By leveraging approaches across projects and predesigning common parts, Stevanato Group has developed flexible modules for operations that are often repeated in different projects. This includes in-feeds, assembly modules, in-process controls, robotics and other elements, such as labelling and packaging. These process modules are then customised according to project specifications and paired to the parent platform, creating a cohesive, fully tailored system.

This approach enables the company to engineer tailor-made solutions that deliver consistent performance and high-quality standards, and opens up the opportunity for greater flexibility to adjust to new device configurations, different device formats or production requirements.

Its modular system architecture streamlines production scale-up, lowers risk and accommodates future expansion, providing long-term value to clients by reducing total cost of ownership and future-proofing their investment.

"Once the assembly process has been validated, it can be easily and rapidly scaled up to meet production demands, minimising risks through early debugging."

CASE STUDY

A recent case study demonstrates many of the key benefits that a proven, integrated partner such as Stevanato Group can bring to a project by taking a holistic view.

As a long-term supplier of primary packaging to Merck Serono, Stevanato Group was engaged to provide highly resistant glass cartridges that could be easily integrated with a pen injector used in different treatments. To help the customer select the appropriate container for their device and processing equipment, Stevanato Group combined its glass expertise with proven testing methods and statistical analysis to establish a viable solution.

By developing a custom testing protocol that focused on mechanical characterisation methods, a comprehensive series of controlled data points was generated for two cartridge products. Performance evaluations and testing of both containers on processing equipment at Merck Serono's site followed. After analysing the results, Merck Serono could confidently select Nexa – a glass product with high break resistance, enhanced cosmetic appearance and tight tolerances that maximise device performance (Figure 2). Furthermore, the analytical team provided recommendations on how to adjust the processing parameters in order to increase the filling line yield.

In addition to these services, Stevanato Group's automation division was commissioned to develop a final assembly solution capable of manufacturing the three different configurations of pen injector. There were high expectations for precision, product quality and throughput.

With its proven linear motion system, Stevanato Group's BasiQX XTV provided

Figure 2: Nexa glass cartridges have an increased mechanical resistance, enhanced cosmetic appearance and tight geometric tolerances.

Figure 3: Linear motion assembly platform customised to Merck Serono pen injector needs.

a reliable and flexible platform for quickly developing a tailored system. Inspection, assembly and labelling modules were configured for the unique processes involved in the project. The result was a cohesive machine with very high precision that was tuned to assemble the different device configurations required. An intelligent layout ensured a compact footprint, a safe working environment for operators and system modularity for future scalability (Figure 3).

> "The result is a state-of-the-art, integrated automation solution that has been supported by the group's expertise in primary containers and analytical services."

Following Good Automated Manufacturing Practice (GAMP) guidance, all incoming materials are checked within the in-feed modules. Rejects are ejected locally to ensure they do not progress further down the line. Labels are verified before application to the final device, which reduces waste by removing the risk of rejecting a fully functional pen due to a misprinted label.

With an emphasis on product quality, the line performs numerous inspection and verification steps, with eight key parameters controlled throughout the process. A combination of cameras, sensors and force position controls are used to detect, verify and pre-orientate components. The dosing mechanism on each pen is tested and, by detecting the exact position of the plunger disc in relation to the cartridge stopper within tenths of a millimetre, each pen can be individually predialled for priming.

Three different pen configurations are handled on the same final assembly machine through a fully automatic format changeover, with the machine changeover time taking less than 10 minutes. No parts need to be physically changed, allowing operators to focus on executing a full line clearance. Equipment highlights include:

- 100% quality control – pens are individually primed to ensure proper dosing
- Highly efficient design – allows three pens with different dose settings to be assembled on one line
- Reduced waste – local reject stations reject only defective components
- Fully automatic changeover – supports flexible production requirements
- Scalable – opportunities to expand equipment to meet future capacity needs.

The result is a state-of-the-art, integrated automation platform that has been supported by the group's expertise in primary containers and analytical services – the combination of which has provided tangible value to an established pharma client.

Commenting on the collaboration, Marcorosario Cusmano, Technical Services Director, Merck Serono Bari Site (Italy), said: "We set the bar very high in terms of both quality and flexibility for this production

Figure 4: Stevanato Group's proprietary and licensed devices portfolio.

line. We partnered with Stevanato Group due to their approach, technology and track record. Now that the line has been commissioned and is starting to operate commercially, I can say that we are very satisfied with the technical implementation and resulting quality that Stevanato Group's integrated approach provided.

CONCLUSION

As combination products continue to grow in both popularity and complexity, the risk placed on these development projects is similarly increasing. To best support project success, Stevanato Group has built upon its foundation as a trusted supplier of primary packaging to add analytical services, automation development, device development and manufacturing services (Figure 4). The integration of these products, knowledge, technologies and services reduces the burden on the pharma partner and de-risks the project, allowing insights and ideas to flow and value to be added at each step.

By providing end-to-end solutions, based on its broad knowledge base and extensive capabilities, Stevanato Group can help customers with the most complex projects. Partnering with a fully integrated supplier such as Stevanato Group provides a platform for deeper dialogue, improved efficiencies, shorter time to market and a single, fixed point of accountability.

"We set the bar very high in terms of both quality and flexibility for this production line. We partnered with Stevanato Group due to their approach, technology and track record. Now that the line has been commissioned and is starting to operate commercially, I can say that we are very satisfied with the technical implementation and resulting quality that Stevanato Group's integrated approach provided."

Marcorosario Cusmano, Technical Services Director, Merck Serono Bari Site (Italy)

ABOUT THE COMPANY

Established in 1949, Stevanato Group is the world's largest privately owned designer and producer of glass primary packaging for the pharma industry. From its outset, the group has developed its own glass converting technology to ensure high standards of quality. The group comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass containers with its brand Ompi; to high-precision plastic diagnostic and medical components; to contract manufacturing for drug delivery devices; to vision inspection systems, assembly and packaging equipment. Stevanato Group also provides analytical and testing services to study container closure integrity and integration into drug delivery devices, streamlining the drug development process. The company is able to offer a range of solutions to biopharma companies for a faster time to market and a reduced total cost of ownership.

ABOUT THE AUTHORS

Lars Keinicke Hansen is Business Line Manager for the Pharma Inspection and Packaging & Assembly at Stevanato Group. He boasts extensive technical experience and management skills to deliver assembly and packaging solutions for the pharma industry. Mr Hansen has a BSc in mechanical sciences from VIA University College in Horsens (Denmark). Before joining the company, he worked as a mechanical engineer and project manager in charge of assembly equipment for insulin pen injectors, assembly lines for plastic syringes and packaging lines for vials, syringes, cartridges and process equipment for catheter production.

Chiara Mussoi is the Product Manager for the Cartridge Platform at Stevanato Group. She is responsible for the development and definition of the go-to-market strategy of glass cartridges (ready-to-use and bulk). After her studies in economics and business administration at the University of Udine (Italy) and Copenhagen Business School (Denmark), she built extensive knowledge working as Product Manager for medical devices for injectable products. Since 2016 – when she joined Stevanato Group – Ms Mussoi has been in charge of evaluating and promoting new products that meet customers' needs and expectations.

Dr Odra Pinato is the Head of the SG Lab Analytics Laboratory at Stevanato Group. She joined the company in 2014 as a protein chemistry expert. Dr Pinato is a pharmaceutical biotechnologist with a PhD in biochemistry and biotechnology. Her academic background is mainly focused on protein chemistry, with two years of post-doctoral experience in nucleic acid biophysics and pharmaceutical chemistry. Since May 2016, she has been leading SG Lab Analytics – Stevanato Group's advanced laboratory focused on analytical chemistry, material properties, and physical and mechanical performance testing of pharma packaging.

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MedPharm

INNOVATION AND AUTOMATION IN TOPICAL FORMULATION DEVELOPMENT

In this article, Marc Brown, PhD, CChem, FRSC, Chief Scientific Officer, Jon Lenn, PhD, Chief Technology Officer, and Charles Evans, PhD, Vice-President of Pharmaceutical Development, all of MedPharm, discuss the challenges faced by the pharmaceutical industry during the development of topical delivery formulations, and how MedPharm's performance testing models help identify and mitigate risks during the process.

TOPICAL PRODUCT DEVELOPMENT

Today, the pharmaceutical market is valued at over US$1 trillion (£764 billion), over 90% of which is in oral or intravenous dosage forms. Naturally, this means formulators have a sound grasp of how to develop these medicines.

Nevertheless, for some drugs, this more conventional delivery is not possible due to drug instability, inability to get the drug to the target site, or systemic side effects, so direct topical application to the target site is required. However, such topical dosage forms are complex to develop and rely upon differing drug physicochemical properties. The formulations are applied to complex biological membranes that have evolved to keep such xenobiotics out. In addition, cosmetic and aesthetic properties of these topical formulations are also critical, as patient compliance is often driven by the ease of use and the application experience.

The global topical market was around $93 billion in 2019, and is forecast to reach approximately $123 billion by 2024[1] with the dermatology market being a significant portion of this market. A 2020 BioPharm Insight report, estimated that there are approximately 900 new products in development for dermatology, split between small molecules (65%) and biologics (35%), with a considerable focus on topicals for the treatment of conditions such as psoriasis, atopic dermatitis and acne vulgaris.

This article focuses on the latest innovation, automation and proprietary technologies that are mitigating the risk of product failure with regard to safety, efficacy and quality in the development of topical products, using dermatological medicines as an example.

> "The global topical market is around $95 billion and is forecast to increase by $70 billion over the next four to five years, with the dermatology market being a significant portion of this market."

MANAGING RISK IN TOPICAL PRODUCT DEVELOPMENT

A company's attitude towards risk fundamentally affects their drug development strategy, which can vary between the development of a simple or prototype formulation (higher risk) or a fully market-ready, commercially viable product (lower risk) to be used in initial preclinical/clinical evaluation. This decision typically

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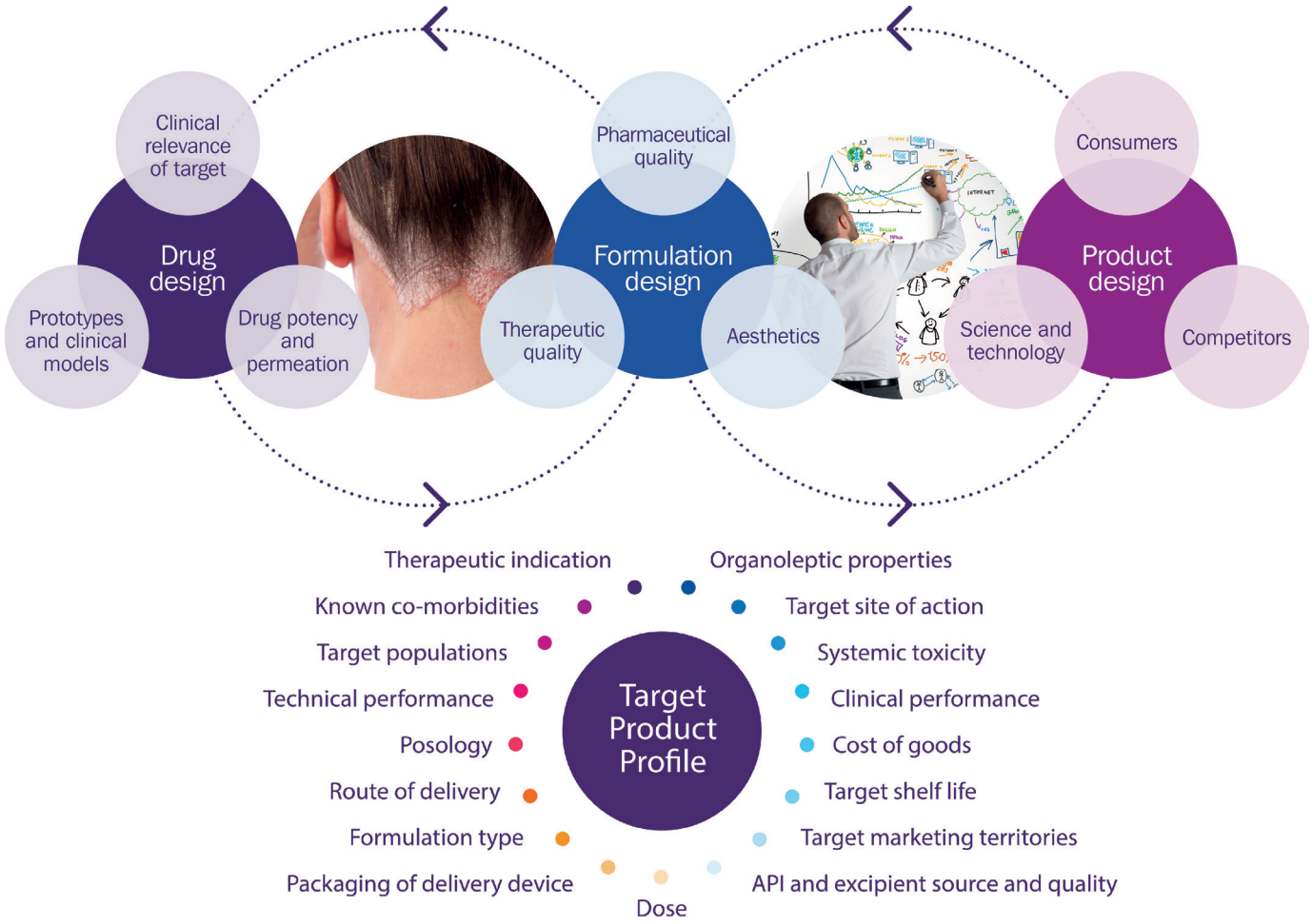

Figure 1: Common considerations for topical product development.

depends on the available funding, target markets and corporate culture. Big Pharma, with many potential drug candidates to prioritise, tends to be more risk-averse, and so generally focuses on entering clinical evaluation with a market-ready formulation that has been developed with risk mitigation considered throughout the development process. For these large companies, early failure is much less expensive than a failure in the clinic.

Conversely, small biotech companies, which may only have a single drug candidate and are typically funded by external investment, often find the development of a prototype formulation more favourable. These small companies tend to be more risk tolerant and prefer to address problems as they arise, in order to evaluate the drug candidate in a clinical proof-of-concept (PoC) study as quickly as possible. In addition, these smaller companies will usually focus on taking their single drug candidate into a formulation development programme for a single geographic market rather than the more universal big pharma approach, e.g. North America, Europe or Japan, which adds a further layer of complexity.

The challenge with this prototype formulation approach is that if the PoC study achieves a positive outcome, further reformulation work is required after the clinical trial to achieve a more patient-friendly and usable product, leading to extensive bridging safety studies. In the worst-case scenario, the formulation development may have to start again in order to proceed to final MAA or NDA. As such, the time and money saved in the early stages is often lost and/or exceeded later in the project. Additionally, any pharma company that is considering in-licensing from, or investing in, a small biotech start-up will always factor in the commercial readiness of the formulation into their due diligence, and the risks of only having a prototype formulation will reduce the market value of their programme.

In MedPharm's experience, the optimal route to success sits somewhere between these two approaches where we leverage our extensive technical and regulatory expertise, proprietary models and state-of-the-art facilities to mitigate the above risks as much as possible, regardless of the financial constraints on the client.

After over 20 years of successfully developing commercial topical products MedPharm emphasises to all its clients that a topical product's 'ease-of-use', aesthetic and cosmetic properties are as important as its efficacy. The selection of a formulation for topical application is influenced by the physicochemical properties of the drug and its potency, the disease to which it is applied and the patient who will use it (Figure 1). As a result, a Quality Target Product Profile (QTPP) should be created to define the key requirements around the quality, safety and efficacy of the drug product. This is an evolving document that is updated as the project progresses where any Critical Quality Attributes influenced by Critical Material Attributes and Critical Process Parameters are identified, monitored, and/or controlled. In parallel, MedPharm always advocates that a risk assessment is performed at these early stages and kept up to date through the entire development process. This inexpensive assessment evolves alongside the project and underpins the ongoing development strategy for the client, regulators and any potential investors.

"MedPharm considers the preformulation stage of a new drug candidate to be the most critical step for topical programmes, upon which the final, optimised, commercially-ready formulation is built."

MedPharm considers the preformulation stage of a new drug candidate to be the most critical step for topical programmes, upon which the final, optimised, commercially-ready formulation is built. For the development of topical drug products, preformulation studies typically involve solubility, stability and compatibility studies with potential excipients to be used in the final dosage form. At MedPharm much of this work is performed using automated and robotic systems. The lowest-risk approach to any submission is to try and keep to excipients, packaging, processes and parameters with which the regulatory authority is familiar. MedPharm always advocates the use of approved and, where possible, compendial excipients, as listed in the Inactive Ingredients Database that are appropriate for use on the disease itself. Once a full understanding of the 'formulatability' of the drug is gained, then a series of formulations can be developed based on the QTPP. Ultimately, for topical products, it is essential that the lead (and any back-up) formulation has been optimised and characterised not only to demonstrate that it will maintain its quality and performance during its entire shelf life, but also to give the formulation the best chance of success in the clinic.

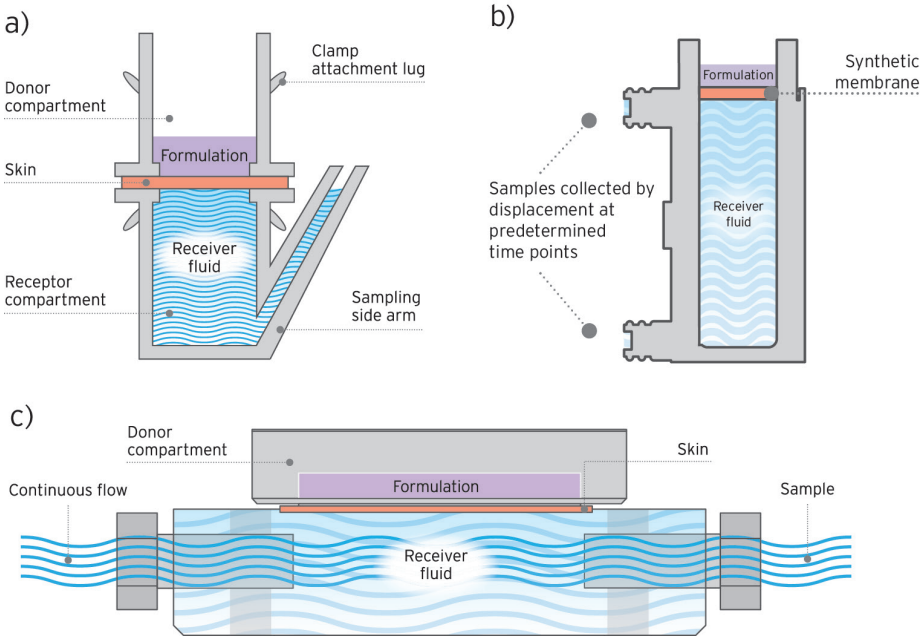

Figure 2: Compared with the industry standard vertical diffusion cells (a) MedPharm's proprietary and fully automated systems, MedStat-HT® (b) and MedFlux-HT® (c) are designed to increase throughput and reduce variability.

PERFORMANCE TESTING: INNOVATION, AUTOMATION AND HIGH-THROUGHPUT SCREENING

Performance testing tools and models provide a way to evaluate new chemical entities, drug delivery, product safety, and the efficacy and quality of topical formulations to reduce their risk of clinical failure, i.e. 'future-proofing'. These tools and models can be divided into four main areas:

1) *ex vivo* pharmacodynamic or disease models
2) *in vitro* (drug) release testing (IVRT)
3) *in vitro* (drug) penetration and permeation (IVPT)
4) product characterisation and stability testing.

As previously stated, one of the major routes of delivery considered for topical medicines is via the skin; some of the biggest advances in dermatology have been with the introduction of biologics for severe skin diseases. These biologics have revolutionised the management of skin disease and have also been instrumental in expanding the basic understanding of inflammatory dermatosis and the discovery of new targets. There is a tremendous amount of effort required to prove that these pathways can be treated with local or topical delivery. This growing interest and understanding in the basic biology of inflammatory dermatosis has led to the development of novel pharmacological disease (PD) models using fresh human skin.

Skin research has a huge advantage in its direct access to large sections of surgical tissue. The latest advances in tissue culture have allowed MedPharm's scientists to keep this surgical skin alive in culture for over a month; thereby creating a living tissue explant. The existing cell population(s) in these explants can be stimulated with specific mixtures to elicit biological responses. MedPharm spends a great deal of time researching specific stimulation conditions (e.g. Th17, Th1/Th2, LPS/PGN, TLRs, etc.), which can be added to these explants to explore different disease states and mechanisms of action, including psoriasis, atopic dermatitis, acne and vitiligo. By combining an increased understanding of immunology, tissue culture and pathway biology these *ex vivo* skin PD models have become critical to the development of new chemical entities and are helping bridge the gap for clinical translation as well as de-risking processes for topical products.

IVRT is used routinely throughout the development process, from the early stages of formulation optimisation and process development, through to scale-up. In addition, regulatory bodies are increasingly requiring its use as a quality tool in release and stability specifications and for demonstrating generic bioequivalence. The majority of industry use comprises an IVRT method based on an open chamber vertical diffusion cell (VDC) system (Figure 2a) fitted with a synthetic membrane as a support for semi-solid dosage forms in order to measure and optimise the drug release from the formulation over time (something akin to tablet dissolution testing). However, MedPharm recently developed a fully automated VDC system (MedStat-HT®) (Figure 2b) that improves on these manual VDCs by providing significant improvements in sample collection, data variation, operator repeatability and study robustness.

Most of the industry uses similar manual VDCs for IVPT studies where the drug is applied to the skin (normally surgically removed), mounted in the VDC (onto which formulation is applied) and the absorption of the drug into and across the tissue is quantified. Such a set-up allows formulations to be optimised and compared, and the risk of not achieving delivery to the pathological site and/or excessive systemic exposure can be evaluated. These systems are notorious for variability and can be challenging for modern lipophilic drugs, making data interpretation difficult. Thus, MedPharm has developed a fully automated flow-through diffusion system called the MedFlux-HT® (Figure 2c) for use in such IVPT studies, which not only dramatically reduces the variability, but more closely mimics the clinical situation compared with the manual static VDCs.[2]

> "MedPharm's use of automation, robotics and higher throughput systems reduces the need for manual operation and enables researchers to deliver more accurate, robust and reliable data to accelerate timelines."

MedPharm's use of automation, robotics and higher throughput systems reduces the need for manual operation and enables researchers to deliver more accurate, robust and reliable data to accelerate timelines. Through the use of liquid handlers and robots, MedPharm can automate steps in preformulation and formulation development to allow drug solubility and stability to be assessed more accurately within various solvents and solvent systems, reducing the risk in variability when compared with manual procedures. When assessing longer-term physical stability, automated instrumentation such as a LUM (Berlin, Germany) LUMiSizer® helps to provide a more accurate prediction of shelf-life compared with the harsher centrifugation technique, where even products on the market are often observed to phase separate. Within process development and scale-up, MedPharm uses IKA (Oxford, UK) laboratory reactors, which provide the ability to control and perform multiple manufacturing parameters at the same time. Assessment of product microstructure (e.g. rheology/droplet size) is quite often overlooked until much later in the clinical phase of development, however,

ABOUT THE AUTHORS

Professor Marc Brown, PhD, CChem, FRSC, Chief Scientific Officer and co-founder at MedPharm, has been the guiding force behind all of the company's scientific developments and intellectual property. Currently he retains Honorary Professorial positions in the School of Pharmacy, University of Reading (UK), School of Pharmacy, University of Hertfordshire (UK), De Montfort University (UK) and the Institute of Pharmaceutical Science, 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.

Jon Lenn, PhD, Chief Technology Officer, has direct responsibility for MedPharm's pharmaceutical innovation and technology strategies and is based out of its facility in Durham, NC, US. Since joining in 2015, he has led MedPharm's development of cutting-edge biological models and tools to evaluate drug product candidates for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience within the pharmaceutical industry developing topical medications for dermatology and, as a result, he has been directly involved with the development and approval of eight marketed products. He received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

Charles Evans, PhD, Vice-President of Pharmaceutical Development, has been with MedPharm for over 15 years and has been heavily involved in evolving and refining the company's rigorous approach to formulation development. Dr Evans has many years of expertise in the successful development of robust commercial products across all types of topical, inhalation and transdermal formulations. Moreover, he played a key role in the development of MedPharm's proprietary MedSpray® technology, which is currently under licence to customers to enhance their products' performance. He obtained his PhD at the University of Hertfordshire (UK) for the development of a novel dynamic spray formulation for the treatment of Athlete's foot.

it is not only key in the development of generic products to show sameness, but also during early phase process development to demonstrate that the process is robust. Such an approach mitigates the risk of failure during clinical manufacture and ensures there are no major changes in product microstructure during the different clinical phases that could potentially change product performance. The consistent and reproducible results on a laboratory scale that can be successfully transferred to larger scales have meant MedPharm has not had any clinical batch manufacturing failures in the last 10 years.

CONCLUSION

Whether via the eye, skin, lungs, nail or other mucosal membranes, it is clear that these alternative topical routes offer key advantages alongside presenting unique challenges. MedPharm's development philosophy forces a rigorous analysis of the product requirements to identify these challenges and de-risk them throughout the development process. MedPharm's formulation strategy builds a formulation specific to the compound. This generates a sound formulation foundation that proactively focuses on creating a final product that will be physically and chemically stable and ready for the clinic. This formulation strategy is coupled with MedPharm's state of the art performance testing models to de-risk potential product failure that may result from an inability to deliver the compound to the target site or elicit a biological response prior to the clinic. This ensures that all risks are identified and mitigated as early as possible to give the product the best chance of success.

ABOUT THE COMPANY

MedPharm is a leading contract provider of topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development times for generic and proprietary pharmaceutical 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 recognised for their scientific rigour by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK.

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INTEGRATING DESIGN AND INDUSTRIALISATION TO OPTIMISE COST, QUALITY AND TIME

In this article, Pete Evans, Director of Device Development at Oval Medical Technologies, and Meredith Canty, Director Drug Delivery Systems at SMC Ltd, explore how integrating design and industrialisation teams can optimise the cost, quality and time of developing a novel drug delivery system.

There is a well-known adage in the pharmaceutical industry: "Cost, quality or time – choose two." In other words, when considering the cost of a development programme, the quality of the end product and the time to bring a new product to market, you have to choose which two of the three to optimise as the third will inevitably suffer.

With quality necessarily taking first place, time and cost are left to fight it out, with time generally being the winner on the assumption that an earlier launch will recoup the increased costs of accelerated development. Because of this, pharmaceutical product development programmes tend to be expensive. Add to this the fact that all product development programmes face quality hurdles, which can take considerable time to resolve, and the costs tend to only move in one direction.

When considering a novel drug delivery system, potentially combined with a novel formulation – and with either element potentially requiring the development of novel manufacturing processes – there are considerable challenges involved in meeting the required quality standard, let alone optimising cost and time.

Based on the principle of developing a deep and long-standing relationship between the two major development teams responsible for bringing a novel drug delivery system to market – the design team and the industrialisation team – Oval Medical Technologies and SMC have established methodologies to manage the risks of creeping time and cost, as well as building quality into the design of a new product, which overcome these challenges.

The development of autoinjectors for challenging applications – whether that be difficult formulations (e.g. high-viscosity liquids, suspensions of insoluble API, non-Newtonian fluids, large delivered volumes, etc) or unusual usage scenarios (e.g. mentally or physically disabled users, military environments, etc) is a speciality of Oval.

By addressing the design restrictions arising from only using glass prefilled syringes as the primary drug container (Oval develops proprietary polymeric systems), placing the needs of the user at the core of the design process and building a comprehensive empirical understanding of the formulation behaviour, Oval is able to design uniquely customised solutions to meet the most challenging requirements.

> "In the early stages of development of a novel concept, there is a balance to be struck between further refinement of the design and commitment to mould tooling."

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Of course, innovative design solutions bring increased development risk – this is where the relationship with the industrialisation team becomes pivotal.

ROBUST DESIGN

As a global contract manufacturer specialising in the development of devices used in the healthcare industry, the SMC team works with the customer to ensure the design is as robust as possible with regard to optimising for the production state. The team will review components, assemblies, overall process flow and the supply chain to ensure items are as optimised as possible. The SMC team will then be responsible for building prototype moulds and assembly equipment to assist the customer in verifying and validating their design. The SMC team can also assist with handling drug product in its primary drug container, as well as complete final kitting and packaging.

In the early stages of development of a novel concept, there is a balance to be struck between further refinement of the design and commitment to mould tooling. Rapid prototyping (i.e. 3D printing) has evolved dramatically in the last 10 years but there is no substitute for real moulded parts. Although rapid prototyping has its advantages in the early stages of the programme, designers need empirical proof that their analytical assumptions are correct – so affordable, rapid mould tooling is usually the answer.

Since there are various levels of rapid prototype tooling, it is critical during the development process that the customer and contract manufacturing organisation (CMO) have detailed discussions to understand the objectives of the rapid tooling (i.e. to test a feature on a part versus to build a prototype tool to mimic the function of a production tool). It is also important to understand the likelihood that certain design features will change.

If the customer and the CMO are not aligned on the expectations of the rapid tooling with regard to tool or part performance, then the wrong type of tool could be produced, either in terms of the mould tool design via over simplification, or in terms of the moulding process with a willingness to accept an over-constrained operating window – or, worst of all, both. This leads to a false belief in the suitability of the design concept that carries through into later stages, where the cost and time required to resolve the problems are amplified significantly.

> "Building an understanding of the potential challenges and starting to plan the assembly strategy before the production design has started brings enormous benefits."

IN-HOUSE RAPID TOOL SERVICE

A typical rapid toolmaker is not interested in reducing the mould cycle time – the tool lifespan is too short to make a meaningful difference – and they are not worried about having to reach into the tool to manually pull out parts that have failed to eject properly. If the parts reach the designers fast, they have met their goal. Any of the learnings arising stay with the toolmaker and rarely make their way back to the design team.

To avoid this, SMC operates an in-house rapid tool service that works closely with the Oval design team from the earliest concept stages of the design process. Tool design centres on a comprehensive set of standard tool configurations that are quickly customised with interchangeable steel inserts to produce each component and provide the correct type of tool/part at the appropriate time. The preferred configuration is agreed upon with experienced production toolmakers who can advise on the best format for the longer term, when increased cavitation and optimised cycle times are the goal. Important choices such as gate position, split lines and ejector locations are also discussed with production toolmakers and these design for manufacture (DFM) considerations fed back to the Oval design team. By investing in proper DFM at this early stage, the prototype mouldings instantly become a far more meaningful representation of the final product.

A SIGNIFICANT SAVING

Of course, design changes are inevitable and, in some cases, components may disappear altogether, with their features or functions absorbed into neighbouring or new components as the design evolves. However, such decisions ought to be made based on the learnings from parts that are representative of production. In those cases where component designs do carry over to the detailed design phase, all the knowledge and experience arising from the prototype tooling brings a significant saving in terms of time, cost and risk for production tooling.

In some cases, when it makes sense, this can even mean that the entire prototype tool can be carried over, simply by manufacturing a dedicated tool base to replace the generic parts from the prototype tooling. The same toolmakers involved in reviewing the prototype tools develop the production tool designs. Additionally, the process engineers responsible for moulding the prototype parts feed back into the design process to ensure any issues are dealt with before any steel is cut, rather than by being forced to run a constrained manufacturing process in the future. All this means the step to production mould tooling is made with greater confidence, less time and reduced cost.

When it comes to validation of production mould tools, accurate metrology of the critical dimensions is fundamental to success. Often, the availability of this data is delayed by misunderstandings between the design and metrology teams. Establishing a common understanding of part function, appropriate points of measurement, design of appropriate fixtures and development of repeatable and reproducible measurement methods all take time. By exposing the production metrology team at SMC to the prototype parts at an early stage, there is the opportunity to start this process early, before the production moulds are made. Advice can be given to the Oval design team on how to incorporate features that simplify fixturing and measurement before the production component designs have even begun. Ultimately this means the tool validation process is completed quicker and with fewer design changes or costly tool corrections.

UNDERSTANDING POTENTIAL CHALLENGES

Of even greater potential benefit is the opportunity to involve the automation experts at SMC in the early stages of design. Building an understanding of the potential challenges and starting to plan the assembly strategy before the production design has started brings enormous benefits. The engineers understand how the device

functions so that when the assembly equipment and process flow are being developed, the team will understand how and where components can be handled and what is critical to the device function.

Introducing a seemingly small design feature further on in development may seem to be straightforward, but making such a change later could invalidate months of expensive tool and assembly validation, as well as functional design verification testing. In all likelihood, the expense of making such a change would lead to pressure to implement a sub-optimal assembly process – increasing the risk of rejects or line stoppages. By contrast, designing the parts with a coherent assembly strategy in place ensures a better yield from the production process – leading to reduced cost of goods.

By introducing this thinking at the prototype stage, it is possible to integrate the DFM and assembly with the metrology considerations and the core functionality of the components in an optimal fashion. Having an automation resource involved early helps plan for the proof-of-principle testing that will be required. It also encourages the team to start thinking about future production assembly methods to ensure the components are designed properly for automated assembly.

INTEGRATED PROJECT TEAM

Good planning is critical and can avoid the obvious problems – but taking on the challenges associated with highly innovative products means unforeseen issues are inevitable. In a poorly integrated team, circuitous lines of communication, administrative red tape and uncertainty over roles and responsibilities can lead to even relatively small problems resulting in time consuming and expensive delays whilst bigger, unforeseen issues have the potential to become terminal.

> "Ultimately, this integrated approach brings together expertise in autoinjector design, injection moulding, quality control and assembly to produce designs."

With a truly integrated project team, where the design team at Oval and the tooling, moulding, assembly and quality teams at SMC all know one another, and roles and responsibilities have been defined, as soon as a problem arises, the established communication lines result in a quick resolution of the issue. The familiarity from running multiple projects together means the personal relationships and established ways of working and communicating that ensure tasks are completed efficiently are in place.

In addition, the growth of the mutual understanding of core technologies and design concepts ensures that each project truly builds on the learnings from the past. From a customer perspective, the integrated nature of the combined team means fewer points of contact, more efficient dissemination of key information and quicker responses to queries or changes in requirements – essentially a more agile and adaptable team.

Ultimately, this integrated approach brings together expertise in autoinjector design, injection moulding, quality control and assembly to produce designs that result in fewer late-stage tool and assembly modifications, more efficient manufacturing and reduced risk of product failures – even in the case of complex devices designed to meet the most challenging requirements. Quality, time and cost can all be addressed in parallel.

> "Good planning is critical and can avoid the obvious problems."

ABOUT THE COMPANIES

Oval Medical Technologies specialises in the development of parenteral drug products, partnering with the pharmaceutical industry to provide bespoke autoinjectors that meet the most challenging requirements arising from diverse patient groups and novel drug formulations. Oval's approach is built around two key areas: establishing a deep understanding of the cognitive, physical and emotional needs of each patient group; and the comprehensive characterisation of formulation behaviours under a range of conditions. With Oval's experience in developing novel primary drug containers, which enables true design freedom, this approach allows it to customise its advanced autoinjector technologies to create truly optimised devices.

SMC Ltd. is a contract manufacturer that is focused solely on manufacturing products for the healthcare industry. Its teams specialise in launching medical devices, diagnostic products and drug delivery devices. The company works closely with customers to review the design of the devices in respect of moulding, tooling and assembly to ensure the design is as robust as possible in production. In addition to moulding and assembly, SMC also offers handling of drug products, final kitting and packaging.

ABOUT THE AUTHORS

Pete Evans has been involved in the development of novel drug delivery devices for more than 25 years, working on inhalers and both pen and autoinjectors. With experience in both consultancy and industry, he has worked in all phases of development – from conception and realisation to validation and industrialisation – for both device and drug/device combination products. As Director of Device Development at Oval, Mr Evans leads a team of scientists and engineers developing innovative injection devices.

Meredith Canty is Director Drug Delivery Systems at SMC and has more than 20 years of experience in the drug device delivery field. Ms Canty has worked on launching a multitude of drug delivery devices – including different style inhalers, manual syringes, safety syringes, dial dose injectors, autoinjectors and wearable devices. Her experience also includes implementing new systems to produce combination products.

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ADVANCED CAPSULE TECHNOLOGIES: DRY POWDER INHALERS TO TARGET DISEASE

In this article, Frédérique Bordes-Picard Business Development Manager for Innovative Products, and Julien Lamps, Product Manager, both of Lonza Capsules and Health Ingredients, discuss the value of capsule-based dry powder inhalers in the modern respiratory market, the factors driving development in this area and considerations for matching a capsule to a device and formulation.

The current prevalence of respiratory diseases is driving a renewed interest in capsule-based dry powder inhalers (cDPIs). Asthma and chronic obstructive pulmonary disease (COPD) are currently the two leading respiratory conditions globally; according to estimates from the World Health Organization (WHO), COPD will become the third leading cause of death worldwide by 2030.[1]

In response, pharmaceutical development pipelines are focusing on creating effective inhalable compounds that are better at treating asthma and COPD than the current market offering. One of the key considerations for this development is the cost of the compound, as WHO data shows that over 90% of COPD deaths are in low- and middle-income countries.[2] cDPIs are recognised for their cost efficiency, patient friendliness and overall effectiveness in delivering dry, inhalable therapeutics. As such, cDPIs are becoming the clear choice for delivering a growing number of these best-in-class respiratory therapeutics.[3]

CAPSULES: DELIVERING INHALABLE ORAL SOLID DOSES SIMPLY & COST EFFECTIVELY

There are a variety of attributes that make DPIs appealing for the delivery of inhalable oral solid doses (OSDs), but cDPIs in particular provide a very strong value proposition from factory to patient. These attributes include manufacturing economies from a cost-of-goods (CoG) and supply chain perspective, as well as the innate patient-friendly ease-of-use, portability and better dose compliance of the delivery method.

Central to the value proposition of cDPIs are the economies and efficiencies related to encapsulating any drug. Along with compressed tablets, capsules are among the most manufactured and best understood dosage forms consumed – and DPIs that use them only expand upon their intrinsic value.

> "cDPIs are recognised for their cost efficiency, patient friendliness and overall effectiveness in delivering dry, inhalable therapeutics."

RESPIRATORY MARKET SEGMENTATION

Drug developers looking to deliver drugs via the inhalation route can generally choose from a variety of different technology platforms. These include:

- Pressurised metered dose inhalers (pMDIs), which are designed to use compressed propellants
- DPIs, which are kinetic, mechanical, dry powder counterparts of pMDIs
- Nebulisers and soft mist inhalers.

Within these segments there is a range of device types, varying from simple and inexpensive to highly sophisticated, more expensive options such as e-devices to improve patient compliance. In practice, drug development is segmenting along these device lines, for example, drug developers are tending to choose pMDI systems primarily for emergency medications like the bronchodilator albuterol.[4]

When considering dry powder inhaler technology, there are three further subdivisions based on how the powder is stored and dosed: capsule, reservoir and blister. cDPIs meter each dose by containing it in an individual hard capsule

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> "In emerging markets, there remains a clear preference for the capsule approach, due to the fact that cDPIs generally provide a means of making certain therapies more accessible."

and then placing in the aerosolisation chamber for delivery. Reservoir devices hold a more substantial quantity of the formulation within the device and generally use a relatively complex mechanisation to meter the dose. Finally, blister-type devices employ a "magazine" fed approach with each dose presented in its individual blister for aerosolisation.

Preference For cDPIs In Emerging Markets

In emerging markets, there remains a clear preference for the capsule approach, due to the fact that cDPIs generally provide a means of making certain therapies more accessible.[5] Asthma and COPD have been underserviced for a long time in these regions. There is significant opportunity to improve the lives of patients by leveraging developments in generic COPD medications and the advantages offered by cDPI-based delivery.

For most developers and manufacturers, capsules are a familiar delivery form with readily available, well-established processes and manufacturing lines. Compared with blister and reservoir platforms, where more dedicated lines are needed and there is a significant leap required in technical knowledge and capex, capsules offer a simpler, more cost-effective route into new markets.

DEVICE COMPATIBILITY

There are many "off-the-shelf" capsule-based DPI devices with different levels of sophistication. Some consist of only three to four pieces, which makes them very cost effective, and many can be customised in resistance, colour and shapes. The way in which a given device opens a capsule can also vary; some devices use one or several needles to pierce the capsule on the side or on the top, while others have blades that slice open the capsule on the side, and some simply separate the body and cap of the capsule. Ultimately, the compatibility between the device and the capsule is a critical factor when choosing the best capsule materials and designs with which to work.

The capsule's structural integrity is of paramount importance. First, the capsule must withstand sudden piercing without shattering. Second, the capsule must be sufficiently robust to take this blow without being crushed – thus preventing distortion or other factors that would inhibit the full dispersion of the capsule's entire contents. Structural integrity is therefore a key consideration for developers looking to ensure downstream patient centricity and support patient compliance efforts with their products. Direct feedback from patients suggests that they are comfortable with loading a device with the medication dose, inhaling and then checking the emptied capsule to ensure the full dose has been taken.

MANAGING FORMULATION-CAPSULE INTERACTIONS

As the formulation needs to be quickly and thoroughly evacuated from both capsule and device, it is important that its contents remain free-flowing – from the point of manufacture to the point of inhalation by the patient. Ensuring the complete and uninterrupted exit of the capsule's contents is an aspect of cDPI that requires focused attention in development. Many existing and in-development DPI formulations tend to be hygroscopic in nature, and as such cause changes in flow properties of the powder.

Interactions between the formulation and the capsule are therefore critical. The properties of capsule materials and the specific characteristics of its polymers can either enhance or diminish the performance of the formulation's flow characteristics. Depending on material and design, capsules can manage a wide range of dry powder formulations, from standard to engineered particles. With the rise of combination products, capsules still present the simplest way of formulating, filling and delivering said products.

> "Structural integrity is therefore is a key consideration for developers looking to ensure downstream patient-centricity and support patient compliance efforts with their products."

Capsule Polymers

There are several choices in capsule type using different polymers suitable for encapsulating cDPI formulations. The most popular include:

- Hard gelatin capsules (HGCs)
- Modified HGCs
- Hypromellose capsules (HPMCs).

The technology and the material science behind capsule and formulation are well understood and capsule manufacturers are offering a number of solutions for cDPI application. Capsules frequently come as a portfolio, allowing developers and manufacturers to customise polymer formulations in many ways – controlling water content is a key consideration for many, due to the trend towards hygroscopic formulations.

HGCs have been successfully used in cDPIs for more than 30 years, during which time they have proved their viability across a broad range of cDPI applications. HPMC capsules, on the other hand, demonstrate excellent properties that address the challenges of some of the newest APIs and formulations, especially towards hygroscopic or water-sensitive formulations that need to be filled under dry environmental conditions.

The two polymers are quite different with respect to both chemical and physical attributes and the choice between the materials is ultimately based on which has the least impact on the formulation. One substantial difference between the two polymers is the amount of moisture in the capsule. Figure 1 shows the results of an internal Lonza study which looked at the differences in water content between two capsule types equilibrated across a range of relative humidities (RHs).

Because many dry powder formulations are hydroscopic or water sensitive, it is not surprising that HPMC capsules have taken a foothold in the cDPI market, given their relative lower moisture content compared with HGC capsules. However, this must be

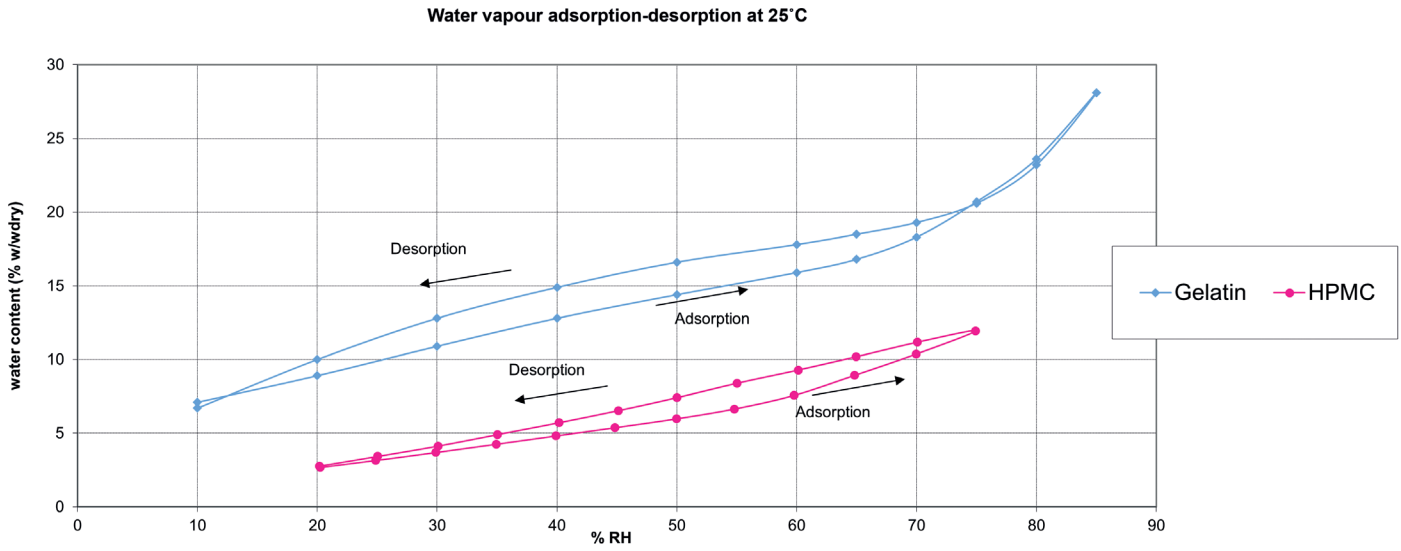

Figure 1: Water vapour adsorption-desorption at 25˚C.

balanced with the triboelectric (electrostatic) properties of the formulation and capsule interface. A dry capsule will exhibit a reduction in dry powder release (i.e. a higher powder retention inside the capsule) primarily due to static charges (Figure 2).

Although dry conditions may be required during filling, as well as within the capsule, to ensure the stability of the API or the formulation, it is important to find the right balance to ensure stability while not excessively impacting the emitted dose. According to the results of an internal study by Lonza, water activity measurements of the formulation can help identify the optimal loss on drying (LOD) target for the capsule.

Regardless of the polymer chosen, best practice recommends that compatibility between the capsule, formulation and device is well established as a first step in a successful DPI formulation drug strategy. It is a necessary step and the earlier that this analysis occurs in development the better.

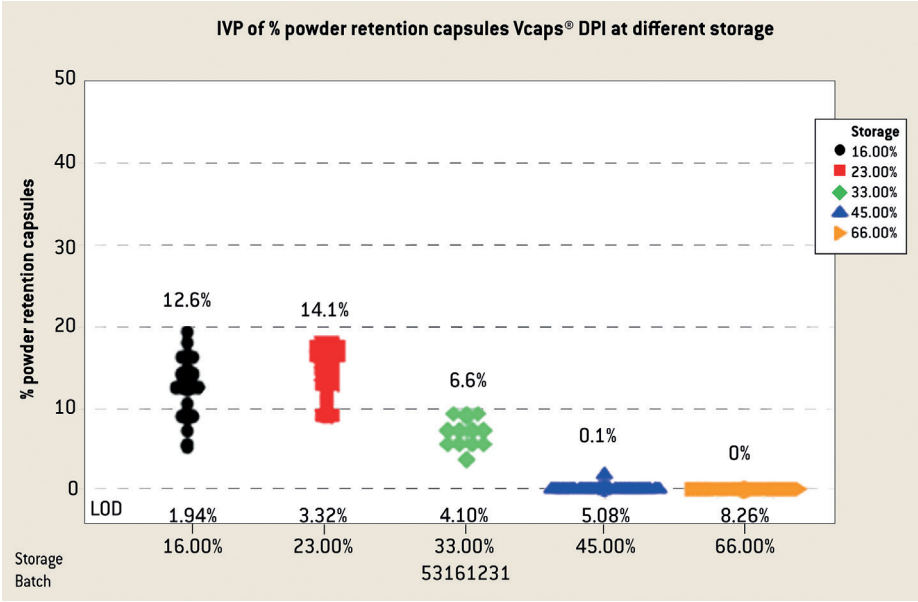

Figure 2: Individual value plot of percentage powder retention in DPI capsules under different storage conditions.

BROADER APPLICATIONS ON THE HORIZON

Capsules are a highly adaptable form, offering a range of customisation options to ensure formulation suitability and flexibility in size, catering for higher dosing requirements. As a result, there is increasing interest in expanding cDPI delivery beyond respiratory indications and to use it for treating diseases such as Parkinson's and Alzheimer's through systemic delivery. There is also notable interest in developing inhalable compounds for nasal/sinus membrane routes of administration for conditions affecting the central nervous system (CNS).[6]

> "There is increasing interest in expanding cDPI delivery beyond respiratory indications and to use it for treating diseases such as Parkinson's and Alzheimer's through systemic delivery."

Looking to the future, cDPIs have become an exciting area of development and look to be an ongoing area of interest for researchers pursuing new chemical entities (NCEs) to treat the unmet needs of a variety of patient groups.[7]

ABOUT THE COMPANY

Lonza Capsules and Health Ingredients is a global capsule and equipment developer and manufacturer which designs and produces innovative products for a wide range of oral dosage forms across the pharmaceutical and consumer health and nutrition market. By combining science, engineering and expertise with innovation and flexibility, the company provides quality products to more than 4,000 customers in over 100 countries and can offer advice on how to achieve customised solutions that optimise formulations and align with project and consumer requirements.

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ABOUT THE AUTHORS

Frederique Bordes-Picard is Business Development Manager for Innovative Products at Lonza Capsules and Health Ingredients. Ms Bordes-Picard is a biochemical engineer by training (Bordeaux Polytechnic Institute), she also holds a Master of Business Administration from KEDGE Business School. Ms Bordes-Picard has been working in the pharmaceutical industry for more than 20 years, first at AstraZeneca UK working on analytical development of therapeutic proteins and antibodies within Bertin Pharma (now Eurofins), mainly on generic product development and licensing out. Ms Bordes-Picard joined Lonza Capsules and Health Ingredients in 2010 as Pharmaceutical Business Development Manager providing technical and regulatory support for new capsule-based product developments. She has developed specific expertise around cDPI product development and filing, supporting multiple companies working on innovative or generic DPI projects.

Julien Lamps is Product Manager for Lonza's Capsule and Health Ingredients business unit, focusing primarily on inhalation and HPMC portfolios. Mr Lamps graduated from Ecole Nationale Supérieure de Chimie de Lille with an engineering degree in chemistry in 2004. He later joined Capsugel as a Quality Assurance Engineer in the Colmar plant in 2011. In this role he worked at the interphase of operations and customers, specialising in co-ordinating new product introductions to develop innovative offers around modified release profiles.

SCHOTT
glass made of ideas

THE FUTURE OF SMART FILL-AND-FINISH

In this article, Diana Löber, Global Product Manager Vials at SCHOTT, discusses new developments in digitised pharmaceutical manufacturing and the role SCHOTT's Smart Containers can play in traceability along the entire value chain.

The industry is constantly looking for solutions to enhance pharmaceutical processes such as fill-and-finish procedures. By taking advantage of the latest developments in machine vision and data science, the pharmaceutical industry can unlock a new era in digitised pharmaceutical manufacturing, which can ultimately lead to levels of automation that have never been possible before.

> "With SCHOTT Smart Container, in each subsequent process step, real-time data can be retrieved and matched with the container."

In a recently introduced approach, known as SCHOTT Smart Containers, individual containers can now be laser-marked with a unique data matrix code at the earliest possible stage in the value chain. This allows for distinct, single-container-based unprecedented traceability throughout the fill-and-finish process and beyond. While the code itself represents a specific numeric or alphanumeric sequence, it is possible to add any relevant data to the code at various points of the fill-and-finish process via a parallel data management system. Each container could be traced, for example during infeed, depyrogenation and filling. Information such as date and time, exact temperature during depyrogenation, retention time in heating tunnel and weight before and after filling could be added to the data matrix code after each step.

Compared with currently available solutions, where this type of data can be collected but it is only possible to match it to an individual container unit after it has been singulated on the fill-and-finish line, this new Smart Containers approach sets itself apart. In addition, after processing using current systems, it is necessary to mark, for example, the cap to keep the data connected with the corresponding container throughout its lifetime. Such workarounds bring other disadvantages. With SCHOTT Smart Container, in each subsequent process step, real-time data can be retrieved and matched with the container. This creates the basis to support the elimination of mix-up risks, optimise lyophilisation processes, improve reject management and line clearance, and foster pinpoint accurate recalls.

> "Using a highly advanced laser to melt the data matrix code onto the container leads to low impact on the glass structure, maintaining the container's strength needed to run on filling lines."

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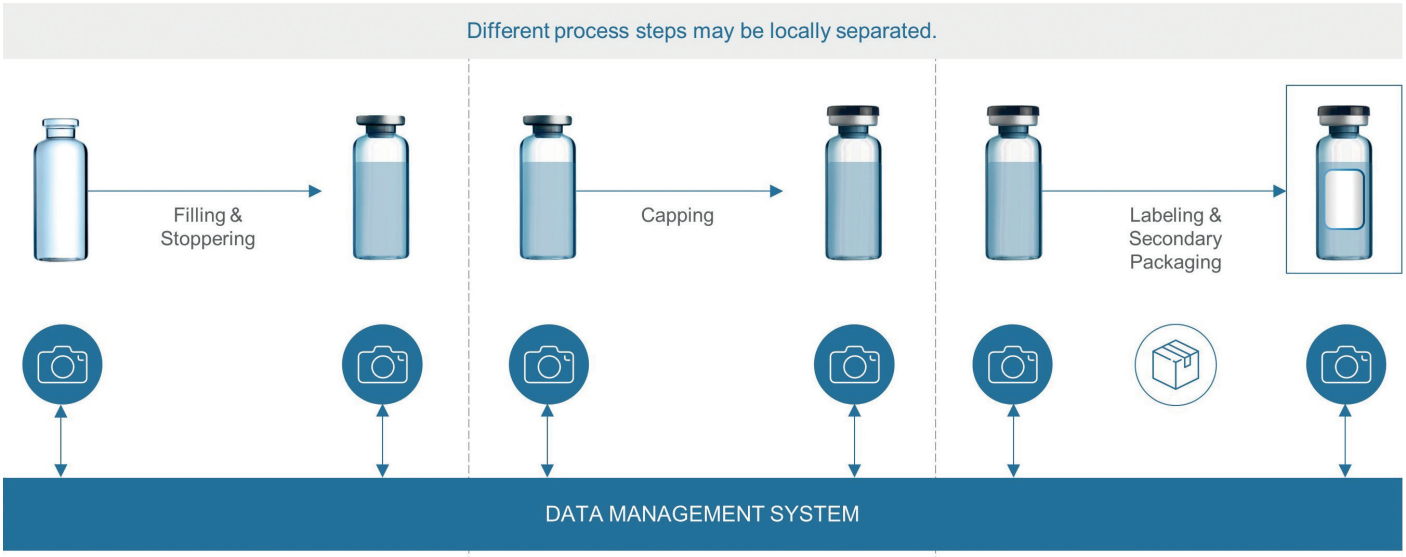

Figure 1: Reducing mix-ups.

THE LASER-MARKED CODE

The data matrix code is based on ISO/IEC 16022 and can be applied in a size of 2 x 2 mm or 1 x 1 mm containing a 14 x 14 dot data matrix. With 16 or 24 digits, the combinatoric possibilities can reach several sextillion possible individual unique numbers. Due to its size and transparency, the code is almost invisible in order to ensure unimpeded inspection by systems or the final user.

Using a highly advanced laser to melt the data matrix code onto the container leads to low impact on the glass structure, maintaining the container's strength needed to run on filling lines. Simultaneously, the code remains stable throughout the entire fill-and-finish process, including washing, autoclaving, and depyrogenation up to a temperature of 600°C. It also resists abrasion and avoids the risk of particle contamination, a key advantage over solutions that require additional substances to be able to apply a code.

For vials, the unique identifier is positioned at the bottom to enable easy readability when the cameras are installed under the fill-and-finish line itself. The positioning at the bottom eliminates the need to rotate the container or to install multiple cameras, as would be the case if the code were placed on the side of the vial.

APPLICATIONS AND ADVANTAGES OF CODED CONTAINERS

Reduced Risk of Mix-Ups

The larger a pharmaceutical company's portfolio of drugs, the greater the risk of mix-ups. This can occur, for example, when the same drug is filled in different concentrations at one filling site, or when numerous steps of the process are performed at various locations, e.g. the vials are kept in storage after filling and before being finally packaged.

Currently, this risk is addressed by methods such as the use of different capping colours. However, the approach is limited by the number of cap colours available and is prone to error. A unique identifier on each container itself, applied at the very beginning of processing, ensures that pharmaceutical companies can now match each container with the right content, cap, label and secondary packaging based on the article data stored in the system (Figure 1). Hence, the content of the container can be identified at any time in the filling process.

Container-Based Targeted Recalls

A recall of pharmaceuticals can cost double-digit million-euro amounts and pose significant risks to pharmaceutical companies. Yet above all, when a recall occurs, it can put human life in danger. Hence, there is industry-wide consensus that recalls need to be handled as quickly and effectively as possible.

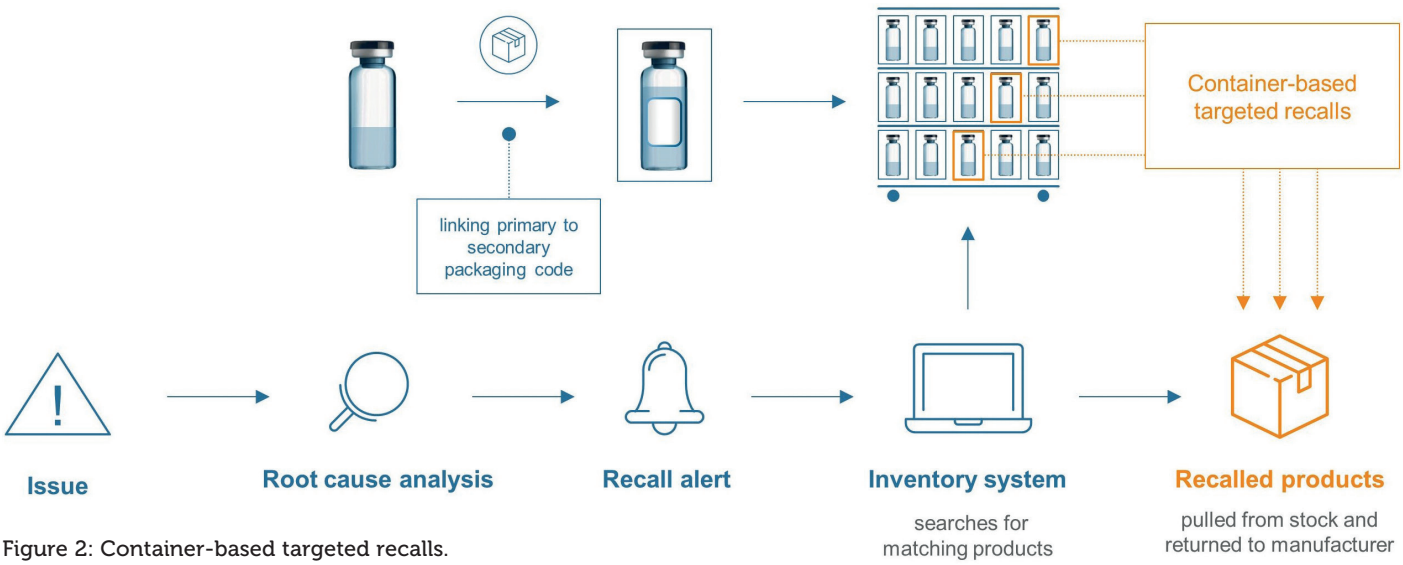

Figure 2: Container-based targeted recalls.

When each individual container is marked with a data matrix code, it can be digitally linked to the secondary packaging code to ensure product traceability at any stage of the supply chain. This can allow a container to be tracked right down to an individual pharmacy's or hospital's inventory management system. In cases when a limited assortment of batches is affected, the corresponding products can be tracked via the inventory system for secondary packaging (which is a regulatory obligation), and withdrawn from circulation (Figure 2), thus narrowing down the recall to save time and reduce costs.

Improved Reject Management and Line Clearance

After each batch production is completed, the fill-and-finish line must be "cleared" for the next batch, which means ensuring that it is free of any material related to the previous batch (e.g. vials, stoppers, caps). This line clearance procedure is mainly performed manually by the operating personnel and is highly time-intensive. However, it does not guarantee the complete removal of remains and subsequently poses a risk.

Currently available IT solutions are capable of generating data at both the beginning and at the end of the fill-and finish process. By doing so, stray containers can be identified. However, with traditional systems, the data cannot be linked to the individual container and it thus remains unclear at which stage of the process the container was lost.

The new approach, comprising laser-marked containers and cameras located at different positions on the filling line, allows each individual item to be tracked throughout the entire fill-and-finish process (Figure 3). In addition, the reason for rejection can be linked to each container in real time. Digitally tracked counts can simplify line clearance by locating the exact spot of any missing container. The increased transparency further supports the employment of corrective actions for smoother reject management and line clearance.

Lyophilisation Optimisation

In the near future, 50% of injectable drugs need to be lyophilised according to US FDA estimations.[1] For pharmaceutical companies this presents another challenge, as freeze-drying is a complex and time-consuming process. Numerous defects such as eutectic melting, cake cracking, collapse, or lifting, fogging, splashing, puffing, or "skin" formation can occur leading to unacceptable products.

It is apparent, that a stable, reliable, tightly controlled lyophilisation process is needed for commercial production. While sensors already exist that measure the temperature of the products in real time, which has the greatest potential impact on product quality, they are only used selectively and often neither the exact position nor the product quality of the vials around them can be tracked.

With sensor-tracked SCHOTT Smart Container vials, the exact position can be determined, as well as the position of surrounding vials. This then allows manufacturers and quality assurance teams to draw conclusions about the lyophilisation process and how to improve it in a timely manner.

THE FUTURE: SUPPLIER DATA ENABLES TRACEABILITY OF CONTAINER-RELATED TOPICS

While the Smart Containers concept already provides a number of advantages, it can be further enhanced in the future. For example, pharmaceutical manufacturers could receive containers that are pre-encoded with the exact information needed. This could include anything from production site, date, time as well as container-related data, e.g. article number, tubing used, quality levels, results of dimensional and cosmetic inspection.

Another option could be to aggregate the data on the label of each tray to simplify incoming inspections. Furthermore, if container-related issues during fill-and-finish occur, these could be linked to the container data received.

A SMALL CODE OFFERS HUGE POSSIBILITIES

In summary, SCHOTT Smart Containers help set the stage for Industry 4.0 in the pharmaceutical industry. The discrete, robust

> "The new approach, comprising laser-marked containers and cameras located at different positions on the filling line, allows each individual item to be tracked throughout the entire fill-and-finish process."

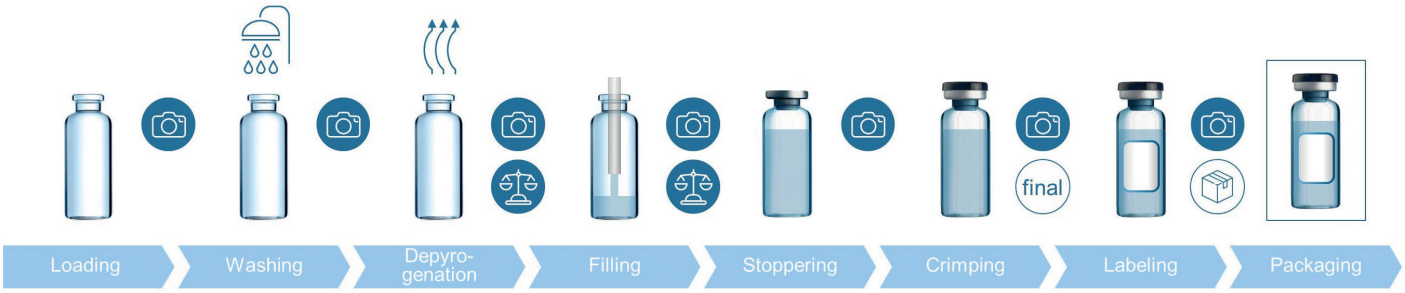

Figure 3: Laser-marked containers and cameras located at different positions on the filling line allow each individual item to be tracked throughout the fill-and-finish process.

and durable code solution that is inextricably linked to the container ensures traceability along the entire value chain. Usage on filling lines is simple and cost efficient, while it does not compromise production speed or create any additional risks. This offers vast possibilities to optimise fill-and-finish operations through improved data management on a single container basis while allowing the user to select what information to use based on the individual's needs.

ABOUT THE COMPANY

SCHOTT Pharmaceutical Systems helps people around the world protect, access and use the medicine they need as safely and conveniently as possible. As a market leader in primary packaging made of glass and polymer, SCHOTT safeguards and advances the integrity of injectable solutions and more. SCHOTT is a pioneer with unsurpassed quality, safety and reliability.

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ABOUT THE AUTHOR

Diana Löber started her career in the medical device industry before she came to SCHOTT in 2018. In her role as Product Manager for bulk vials, Mrs Löber is responsible for product strategy, including the identification of new market opportunities and the development and launch of innovative products.

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