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Nov	Pulmonary & Nasal Drug Delivery
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Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery
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Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery

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Front cover image, "Industrial production of pMDI canisters" supplied by Recipharm AB (see this issue page 20). Reproduced with kind permission."

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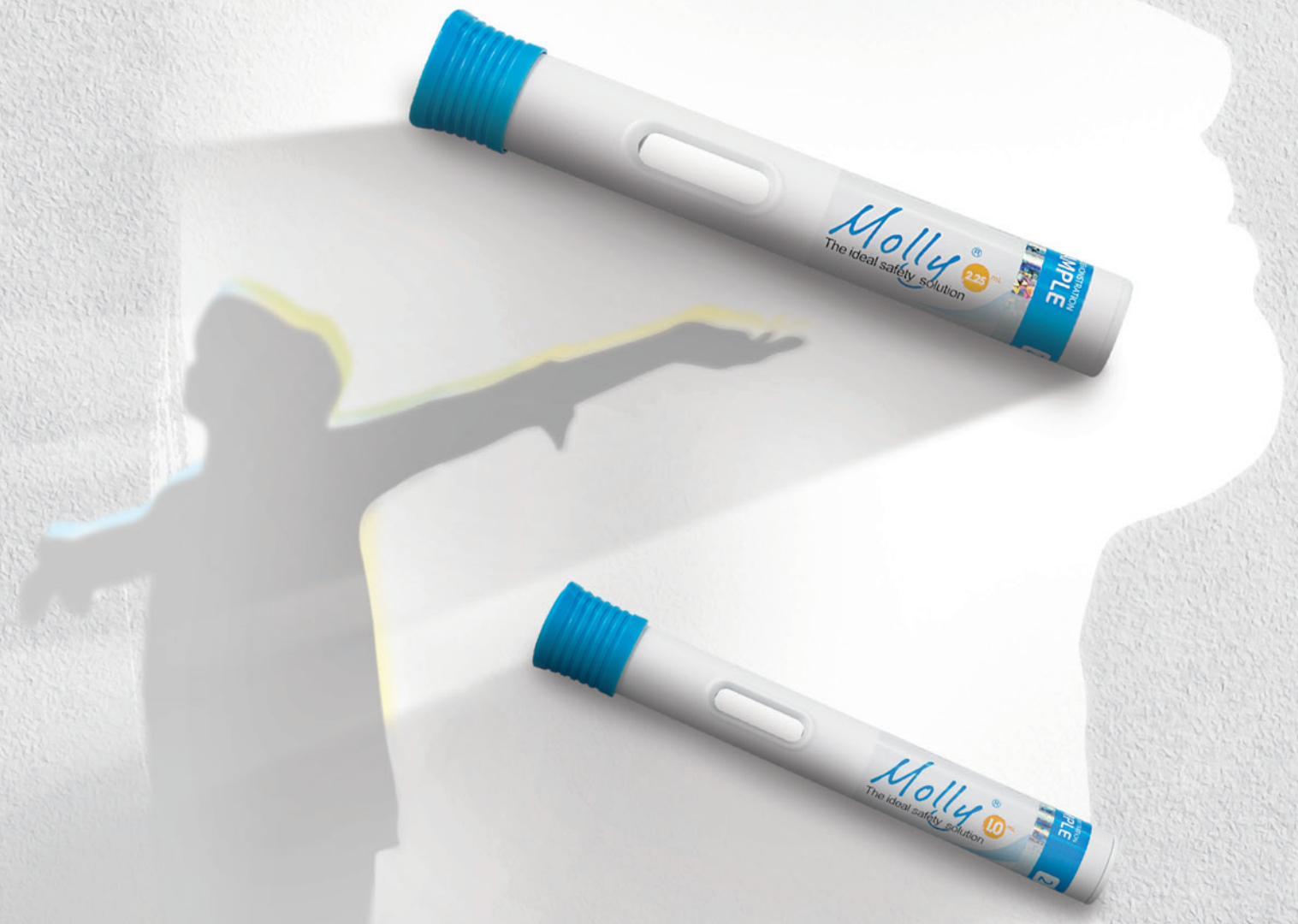

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EXPANDING AUTOMATION CAPACITY FOR HIGH AND LOW VOLUMES

In this article, Gilbert Fluetsch, Director, Automation System, and Lucy Chung, Director, Automation System, both of SHL Medical, look at how automation and assembly services can best evolve and adapt to industry standards and market demands, whilst delivering consistently at high quality and in a timely manner.

With the technological advancement of autoinjectors, the increasing development of biologics and the growing popularity of home-care self-injection, the demand for autoinjectors continues to flourish.[1] Pharma companies are now increasingly in a race to launch their products to market, and suppliers need to align with pharma's development speed, delivering rapidly whilst maintaining high quality standards.

Having been one of the major players in the drug device industry for 30 years, SHL knows all about the shifting demands in the autoinjector markets. Initially, SHL's manual and semi-automated manufacturing capabilities were sufficient to fulfil low- to medium-volume device orders that covered just a few therapeutic areas. These capabilities also provided customers with a level of flexibility for clinical or commercial needs. Today, autoinjectors have become one of the more prevalent solutions for self-treatment of biologics, and both the range and number of demands are increasing.

> "Collaboration between machine builders and device designers in the initial stage of device development could significantly increase productivity since designers have first-hand knowledge of designing components most suitable for automation assembly."

When multiple customer demands require a production output of millions of devices per year, there is an increasing need to scale-up manufacturing production. Consistent quality that meets the highest regulatory requirements also needs to be addressed when scaling-up. Automated assembly machinery offers the reliability to produce high-volume productions with identical quality from the first assembled unit until the last unit. SHL has a strong knowledge base – from multiple electronic and software engineers and experienced project managers – when it comes to building automatic assembly machines for autoinjectors. Each machine system is fully researched and customised for multiple automation requirements.

To achieve the specified design requirements for the manufacturability of an autoinjector, SHL's cross-functional teams of industrial designers, assembly system engineers, tooling engineers and moulding operations must collaborate closely to deliver satisfactory results. For example, the automation department must assess whether components are applicable in bowl feeders for assembly production, then collaborate with design teams to develop the precise specs of a component for automated assembly.

SHL's strength in developing in-house automation lies in the parallel development process across numerous departments in one organisation. This means the design,

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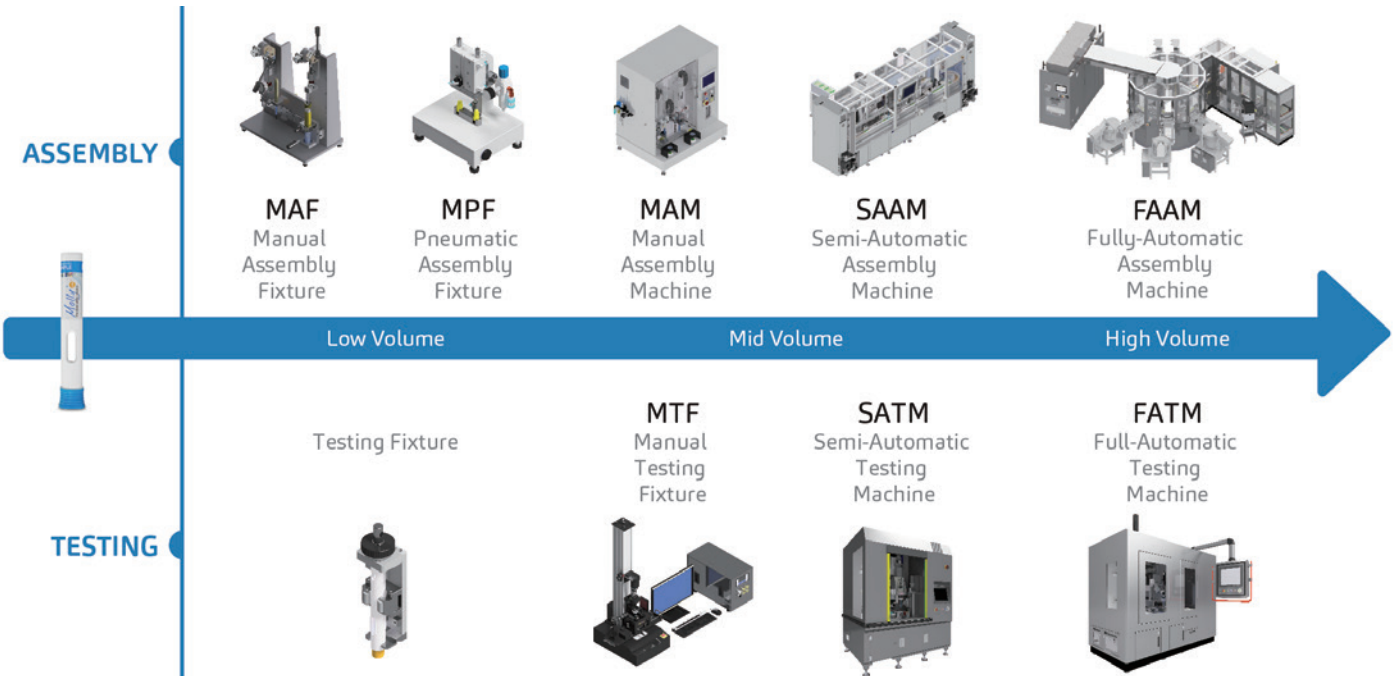

Figure 1: SHL's automation system department machine offerings.

tooling and automation phases all begin development at an early stage. For the automation department, collaboration between machine builders and device designers in the initial stage of device development could significantly increase productivity since designers have first-hand knowledge of designing components most suitable for automation assembly. Streamlined communication across departments increases production efficiency and eliminates potential risks that might occur during a linear process.

Failure modes and effects analysis (FMEA) and process failure mode effects analysis (PFMEA) carried out in close collaboration between the device design, quality, manufacturing and risk teams are also an important advantage in establishing an in-house automation department.

With the ability to design and manufacture assembly and testing equipment in-house, SHL's automation department offers a wide range of manual, semi-automatic and fully automatic machine systems. Assembly requirements for manual and fully automated equipment vary greatly.

In general, SHL's automation department addresses two core capabilities – assembly and testing. Within these two main categories, SHL offers sub-assembly and final-assembly machine systems, as well as final device testing and sub-assembly testing services (Figure 1).

The design and development process of SHL's automated equipment complies with a standard procedure which includes the definition phase, the engineering phase, the manufacturing and assembly phase, the debug and final test phase, and the shipping phase (Figure 2). Regarded as the most critical step, the definition phase demands top-level clarification and a fully agreed set of specifications to ensure the successful flow of future operations. In other words, to alter a drawing or the module of a machine on a 3D CAD drawing is unquestionably more achievable than replacing or modifying parts on an actual machine.

> "A strong project management department ensures projects stay within the specified time frame and budget."

A strong project management department ensures projects stay within the specified time frame and budget. Mechanical and software engineers transform ideas into reality by following systemised procedures and guidelines that determine the accuracy of the developed equipment. These machines are developed in accordance with the provided designs and processes that comply with the requested GAMP5, ISO 9001 and CE standards.

Another important factor in the development process is software validation. Stringent validation processes are

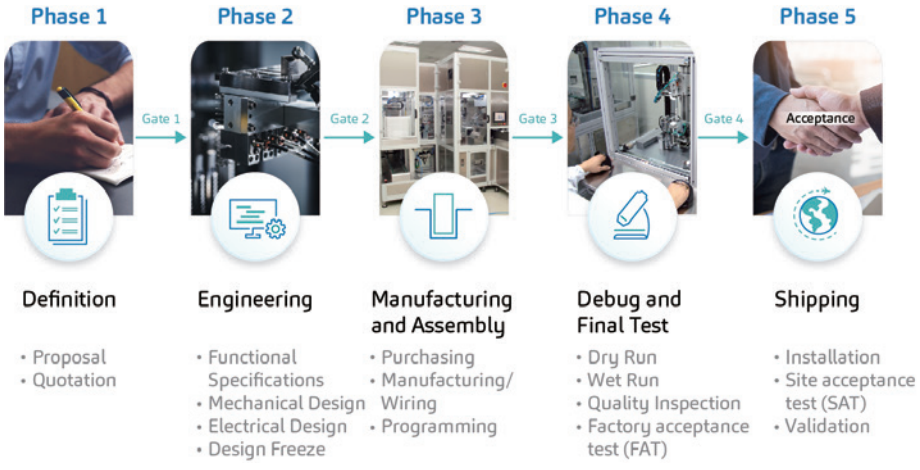

Figure 2: The design and development phase (gate control) of SHL's automated equipment.

implemented to meet FDA 21 CFR Part 11 regulations. Furthermore, in-house service engineers provide on-site maintenance and services to SHL's assembly and test equipment to ensure continued operations without issues in a 24/7 work environment.

THE MODULAR APPROACH

In an effort to produce high-quality and high-volume output, SHL introduced a modular design approach to the equipment base. With this, SHL is able to provide a standardised platform to build high-, medium- and low-volume output equipment. The modular design regarding manufacturing equipment also means a repeatable system that can be used in several production lines. This repeated method supports SHL's goals to drive down costs, reduce risks, shorten lead times and increase production efficiency.

Modularisation in assembly allows for the standardisation of key manufacturing machinery and processes. The benefits include increased production efficiency, reduced costs and a faster output rate.

Designing a modular platform for multiple functions has its challenges. For instance, a final device consists of less than five parts that need to be assembled; in comparison, a sub-assembly consists of anywhere from four to 15 individual moulded or metal parts. The contrast in the number of parts between these two major units poses a challenge in designing an all-standard platform that supports both functions. Furthermore, the process and assembly requirements for a sub-assembly are quite different from a final assembly.

SHL owns the capacity to overcome such challenges and has designed multiple modular platforms that could serve as the base for both automated final assembly machinery as well as sub-assembly machinery.

INCREASED FLEXIBILITY

Another example of a modular design approach is SHL's multi-device equipment strategy, designed to assemble a higher mix of devices on the same equipment. This "low volume/high mix" idea also supports SHL's goals to help customers reduce costs or other additional investments. For instance, building an assembly machine for low-volume batches would include additional design and development time for brand new equipment as well as unwanted idle time for the machine. The process can be compared with building a machine from scratch, having it operate for a few hours, and then having it sit around all day. With a modular platform designed with interchangeable fixtures and grippers, however, SHL has the ability to operate a variety of devices or several different versions of the same device on the same machine. This significantly reduces the equipment idle time, saving time and resources. That way, the machine can run 24 hours a day while supporting a diversified range of offerings.

The multi-device equipment strategy signifies SHL's flexibility to meet several market demands, especially for customers with bespoke product specifications. Although the most perfect scenario would be to operate on modular platforms with high-volume production, the industry requires SHL to adapt and raise its standards of flexibility.

BEYOND HIGH-VOLUME DELIVERIES

The importance of offering a more flexible automation programme beyond high-volume production lies in the propensity of the rapidly changing medical device industry. Drug products experience numerous clinical trials, pilot market testing, user feedback or even regulatory issues that could well cause an impact on the quantity of

> "Drug products experience numerous clinical trials, pilot market testing, user feedback or even regulatory issues that could well cause an impact on the quantity of an order from a customer."

"Using modular platforms reduces the complexity of redesigning a new testing machine and further reduces the risks that might occur during the design process. The more streamlined an operation is – and the less manual input required – the fewer chances for mistakes to happen."

an order from a customer.[2] Some customers would opt for lower volume production to reduce risk and investment. Therefore, with regards to the varied market needs, raising the capacity for high-quantity developments would not always be the accurate response.

Contrary to high-volume production output with singular, dedicated processes without needing changeovers, low-volume production output requires several dedicated processes to support the flexibility in manufacturing. By interchanging several components on one singular machine – or strategically mixing and matching different module types – SHL ensures the reusability of a modular system for the vast and often varied demands from the client.

This significantly expands its capabilities in providing a wide range of deliverables in different quantities, building confidence among customers with varied market needs.

AUTOMATING TESTING PROCESSES

With such stringent quality standards, SHL pays detailed attention to the testing of autoinjectors. Comprised of a primary container and 15–20 components of plastic and metal material, an autoinjector calls for several items to be tested to ensure safety for end users. Such is the complexity in the mechanism of an autoinjector, in particular when the moment of activation includes the sudden release of a spring force that drives the needle forward into the skin.

For device testing, SHL offers an integrated testing system that is applicable for both autoinjectors and pen injectors. The system's configurability to the user's preferences helps ensure the device meets its usability requirements, while detailed data analysis of multiple test items expands the scope for future product research and development. SHL also offers fully automatic testing equipment for mass-produced devices, with customisable options in terms of hardware and software for the convenience of the user. The equipment offers stable test parameters whilst supporting various test devices.

In response to high market demand, SHL has also approached the testing systems with modular designs, offering faster changeovers, ease of configuration and heightened flexibility. The importance of leveraging modular designs in testing equipment is significant in reducing lead times and risks. The test items of an autoinjector vary according to the device's proprieties – with the number ranging from 10-20 items. Using modular platforms reduces the complexity of redesigning a new testing machine and further reduces the risk that might arise during the design process. The more streamlined an operation is – and the less manual input required – the fewer chances for mistakes to happen.

In terms of reducing lead times, a modular platform eliminates the need for particular revalidation processes due to its redundancy. By altering a few component or equipment parts to accommodate test devices, the modular platform ensures a smoother process in testing procedures – significantly reducing the production timeline for customers and ensuring a speedy delivery for SHL. Moreover, the "low-volume/high-mix" strategy also applies to modular testing equipment, adding further value to the modular programme when lower-volume output is required.

Regarding SHL's offering, the company's automation and assembly services will continue to support the needs of its customers, by evolving and adapting to industry standards and market demands, while promising output of high quality and consistent, timely delivery.

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 more than 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.

ABOUT THE AUTHORS

Gilbert Fluetsch joined SHL's Automation System Department (AMSD) 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).

Lucy Chung is the director at SHL's Automation System Department (AMSD) and is responsible for overseeing equipment design, development, manufacturing and overall production quality. Prior to this, she held roles in project management, operations and customer service in AMSD. As one of the first few employees of SHL, Ms Chung was instrumental in establishing product testing and quality systems for the company. She has a BS in Industrial Engineering from National Taiwan University of Science and Technology.

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Publication Month	Issue Topic	Materials Deadline
September 2019	Wearable Injectors	PASSED
October 2019	Prefilled Syringes & Injection Devices	Sep 5, 2019
November 2019	Pulmonary & Nasal Drug Delivery	Oct 3, 2019
December 2019	Connecting Drug Delivery	Nov 7, 2019
January 2020	Ophthalmic Drug Delivery	Dec 5, 2019
February 2020	Prefilled Syringes & Injection Devices	Dec 23, 2019
March 2020	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 6, 2020
April 2020	Pulmonary & Nasal Drug Delivery	Mar 5, 2020
May 2020	Injectable Drug Delivery: Formulations & Devices	Apr 2, 2020
June 2020	Connecting Drug Delivery	May 7, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
August 2020	Industrialising Drug Delivery	Jul 2, 2020
September 2020	Wearable Injectors	Aug 6, 2020
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020

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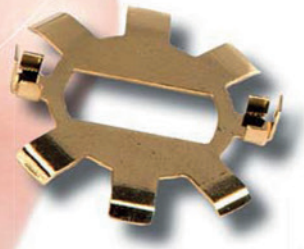

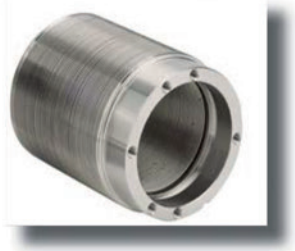

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3D PRINTING DRUGS: LEARNING FROM THE PIONEERS

In this article, Jamie Clayton, Operations Director, Freeman Technology, reviews the potential of 3D printing as a pharmaceutical production method and looks at the associated implications for formulation development, focusing on powder-based printing. He examines what leading experts now understand about how to specify powder feeds for 3D printing, referencing experimental data, and highlights the importance of powder-flow characterisation in this context.

In August 2015, the US FDA approved SPRITAM®, the first 3D-printed drug, for the treatment of seizures in adults and children with epilepsy. Manufactured on a platform that traces its heritage back to technology originally licensed from MIT (Cambridge, MA, US), this approval is useful in providing clear evidence of the possible benefits of printing drugs. These include the potential to deliver very high drug loadings and to produce highly porous tablets that disintegrate rapidly on contact with minimal amounts of water, and successfully delivering drugs to patients who have dysphagia (difficulty swallowing) and/or struggle with conventional tablets.

Beyond these established benefits, the industry continues to debate and explore the possible long-term role of 3D printing in the delivery of personalised medicine, for example, and in localised manufacture. 3D printing offers exciting flexibility to tailor the size, drug-release profile and shape of oral solid-dosage forms, a defining generic benefit of the technology being the minimal cost of bespoke manufacture. Once a printer is in place, making a new product can be as simple as switching raw ingredients and selecting the required operating protocol.

The core attractions of 3D printing are obviously not uniquely interesting to the pharmaceutical industry; in fact, other sectors are more advanced in embracing this innovative technology. 3D printing is now well established for finished part production in the aerospace and automotive sectors and, more relevantly, is widely used in medical engineering – for example, for the construction of artificial bones and dental implants. As the pharmaceutical industry begins its exploitation of 3D printing, it seems sensible to consider what can be learned to accelerate progress.

EXPLORING THE POTENTIAL OF 3D PRINTING

The vision of pharma manufacturing potentially enabled by 3D printing is one in which pharmacists will ultimately switch from dispensing uniform, ready-made products to printing drugs to order, accounting for factors such as genetics, age, gender, and biochemical and disease profile.[1,2] Such a transformation would present significant regulatory challenges but, at the same time, it offers substantial opportunities to tailor therapeutic regimes cost effectively to increasingly small population groups – for example, to treat paediatrics and/or geriatrics more effectively and to tackle orphan diseases. Personalisation is the ultimate endpoint of such a process and could significantly enhance clinical outcomes, even with existing drugs.

On-demand prescription printing would reduce the need for products with extended shelf life. It also offers opportunities to improve patient compliance (the so called "pill burden") through the use of polypills – dosage forms containing multiple actives that are printed to individual patient requirements. For developed economies, 3D printing has potential as a highly efficient,

"The vision of pharma manufacturing potentially enabled by 3D printing is one in which pharmacists will ultimately switch from dispensing uniform, ready-made products to printing drugs to order, accounting for factors such as genetics, age, gender, and biochemical and disease profile.[1,2]"

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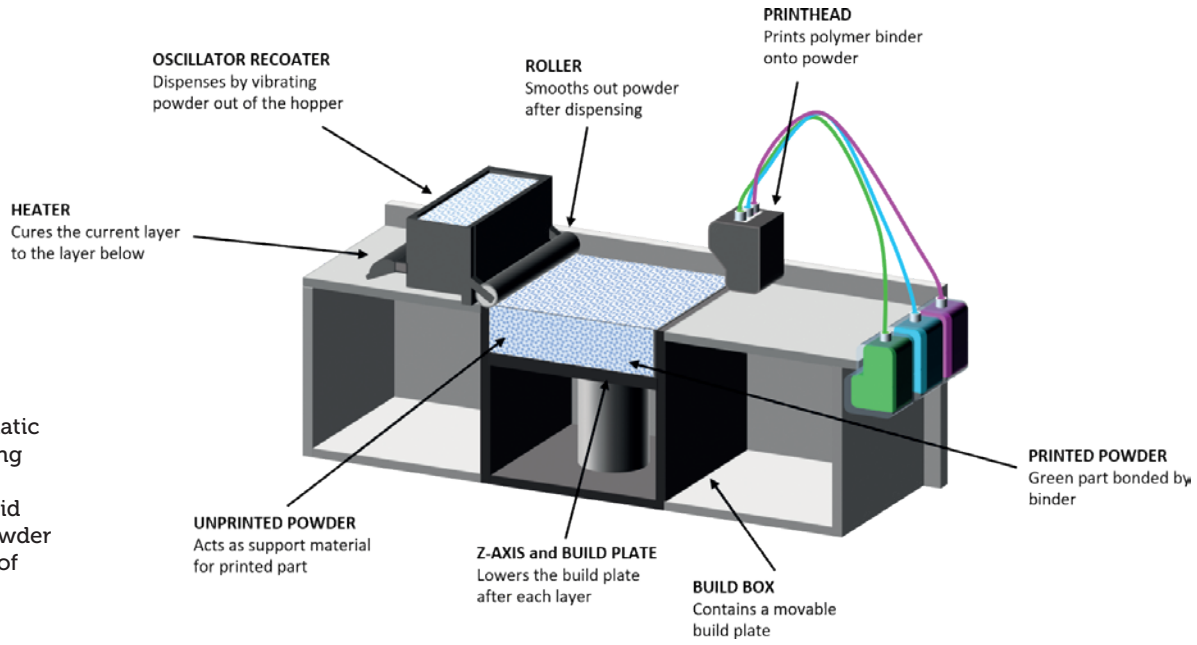


Figure 1: Schematic of a binder jetting process which involves the rapid spreading of powder layers just tens of microns thick.

agile platform for domestic production, to reduce exposure to geopolitical risk and supply chain disruption, while for remote, poorly connected communities it provides relatively low-cost access to high-quality, well-manufactured drugs.

So, how close are we to realising this vision?

The approval of Aprecia Pharmaceuticals' (Blue Ash, OH, US) SPRITAM® is undoubtedly an important milestone and the ZipDose technology that underpins it is now being more generally promoted for the rapid delivery of high drug loads and/or multiple APIs. Dose sizes are two to three times higher than can be delivered via conventional orally disintegrating tablet (ODT) technology, dispersion times are generally faster and the technology offers considerable versatility for taste masking. The potential for brand extension provides a stimulus for technology uptake.[3]

With respect to on-demand printing, FabRx (see this issue, page 28) – a spin-off company from University College London – has recently been awarded funding to develop the world's first 3D printer for personalised medicines. The aim is to develop a printer that will be safe and fit for purpose to produce printed tablets ("printlets") in a hospital pharmacy setting. Work on patient response to 3D-printed tablets is also underway, with the world's first paediatric trial currently taking place at Alder Hey Hospital (Liverpool, UK). Within two years this team plans to transition from testing placebo products to those containing an active pharmaceutical ingredient (API), focusing on hydrocortisone which is currently dosed in poorly controlled levels because of the need to break up pills to give children a weight-related dose.[2]

> "One area of focus is the identification of critical material attributes for excipients for 3D printing and the development of correlations between material attributes and product performance."

On the regulatory front, the US FDA's Center for Drug Evaluation and Research (CDER) is actively engaged in research to address questions raised by using 3D printing specifically for drug products, recognising that progress in this area will be crucial.[4] One area of focus is the identification of critical material attributes for excipients for 3D printing and the development of correlations between material attributes and product performance. This is a major focus for those working to exploit the technology commercially too; optimising pharmaceutical formulations for printing is a new challenge.

AN INTRODUCTION TO 3D PRINTING TECHNOLOGY

Technologies that can be used to print pharmaceuticals include material extrusion processes such as semi-solid extrusion, which is suitable for printing gels or pastes, and fused deposition modelling – the construction of products from a pharmaceutical-grade polymer filament. Stereolithography, a process from the vat photopolymerisation family, can also be applied. This involves using a laser to cure layers of liquid polymer, with API incorporated into the emerging polymeric network. The focus of this paper is powder-based processes such as binder jetting – the powder-liquid technology originally developed by MIT – and powder-bed fusion (PBF), alternatively known as selective laser sintering. These both involve the joining of successive layers of powder to construct the finished dosage form (Figure 1).

In binder jetting and PBF processes, the formulation is delivered or spread across a build surface in layers just tens of microns thick. With binder jetting, a printhead then releases droplets of liquid/polymeric binder into the powder bed, which are thermally cured to bind defined areas, progressively building the dosage form layer by layer. PBF processes are strictly analogous but powder layers are fused through the application of heat, using a laser, which obviously has implications with respect to the protection of thermally labile drug substances; curing is a lower temperature, far less energy intensive process.

FORMULATION CHARACTERISATION: FOCUSING ON FLOWABILITY

When characterising pharmaceutical formulations for 3D printing, there are lessons to be drawn from experience of conventional tableting processes and from those already applying 3D printing in other sectors. This is especially true with respect to the best methods to apply for bulk powder testing, specifically the measurement of powder flowability – a property of defining importance in both processes.

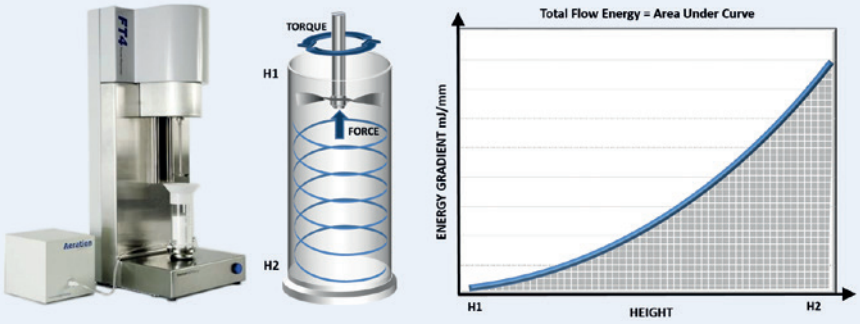
In a conventional direct compression tableting process, raw ingredients are dispensed from feed hoppers at a consistent, closely controlled flow rate into the mixing stages that precede granulation, where used, or directly into the feed frame. In a hopper, raw ingredients are subject to compressive storage under their own weight, resulting in moderate stress at the discharge outlet. Granulation of a tableting blend is extremely common, to prevent segregation and improve flow properties, with flow additives routinely incorporated to further enhance flowability throughout the process.

Powder flows from the feed frame in a relatively loosely packed, low stress state and is swept into the dies to ensure a complete fill. This sweeping action can exert an element of forced flow, with blades pushing the powder into the confined die space. Air can have a lubricating, enhancing effect on powder flowability but uniform filling, to a defined bulk density, calls for a formulation that settles rapidly, easily releasing entrained air. The final step of conventional tableting is compression followed by ejection from the die.

Shear cell testing was developed specifically to quantify powder properties for hopper design and remains valuable for investigating behaviour under the moderate stress that prevails in storage. However, flow behaviour in other areas of the traditional tableting process are more successfully predicted by dynamic testing[5] (see Box 1). Basic flowability energy (BFE), for example, is highly relevant for rationalising performance in the feed frame, while measurements of AE valuably quantify how flowability changes with air content.

BOX 1: AN INTRODUCTION TO DYNAMIC POWDER TESTING

Dynamic powder properties are determined from measurements of the axial and rotational forces acting on a blade, or impeller, as it is precisely rotated through a powder sample (see image). The technique was developed specifically to measure powder flowability under conditions that simulate the process environment and powders can be measured in a consolidated, moderate stress, aerated or fluidised state. This ability to tailor the test environment, particularly with respect to direct assessment of the impact of air, sets dynamic testing apart from traditional USP methods. Furthermore, the technique offers exemplary repeatability, reproducibility and sensitivity.



Dynamic testing measures the powder in motion and can be applied to samples in a consolidated, moderate stress, aerated or even fluidised state.

Dynamic properties include:

- *Basic flowability energy (BFE)* which quantifies confined flow behaviour (forced flow) in a low-stress powder and is measured during a downward traverse of the blade
- *Specific energy (SE)* which quantifies the unconfined flow properties (gravity flow) of a powder in a low-stress state and is measured by rotating the blade upwards through the sample
- *Flow rate index (FRI)* which quantifies sensitivity to flow rate and is determined from measurements of BFE at different blade speeds
- *Stability index (SI)* which quantifies physical stability and is determined from repeat measurements of BFE on the same sample
- *Aeration energy (AE)* which quantifies the impact of air on flowability via measurements of BFE at a defined air-flow rate through the sample.

Instrumentation for dynamic testing also measures shear and bulk powder properties, such as permeability and compressibility, which characterise the ease with which the formulation releases entrained air and its response to compression, respectively. As a result, it is able to provide the multi-faceted insight needed to optimise tableting processes.

The initial feeding of raw ingredients from a feed hopper into a 3D printing process is similar to a conventional process, so shear data remain relevant. However, the powder then transitions into a low stress environment with high flowability under such conditions essential for the sequential deposition of powder layers. Indeed, in 3D printing, processing rate is effectively defined by the ability of the powder to consistently form even layers of defined thickness; dynamic flow properties are valuable for defining performance with respect to this crucial aspect of behaviour. As with die filling, the goal is a layer with minimal or controlled voidage since voids inhibit fusing/binding, ultimately impacting the mechanical integrity of the finished product; bulk density measurements can be helpful in rationalising packing behaviour.

An important point to appreciate about 3D printing is that only a proportion of the powder in a given layer is bound into the finished product; powder recycling is therefore vital for sustainable manufacture. This makes the stability of 3D formulations an important issue. The characterisation requirement is to understand the behaviour of both fresh/virgin and recycled material, with properties potentially changed by the printing process. Dynamic test protocols for stability can be extremely useful in this regard.

KNOWLEDGE TRANSFER

Reviewing practice in industries in which 3D printing is more commercially established is illuminating in terms of the specifications already in place to identify powders that will print successfully. ExOne (Pittsburgh, PA, US) is a global leader in binder jetting technology. In 1996, the company obtained the licence for the 3D-printing process developed at MIT for metal and sand parts and it has since gone on to develop and commercialise technology with applications in the automotive, aerospace, heavy industry and energy sectors.

Over several years, ExOne has progressively refined the specification

	Powder A	Powder B
D_{10} (µm)	6.4	6.6
D_{50} (µm)	16.1	15.8
D_{90} (µm)	29.1	30.0

Table 1: Data for two alternative supplies, illustrating the strength and application of the powder specification. Powder B, an alternative supply, is less expensive than Powder A; testing was being carried out to determine whether a switch could be made to enhance profitability.

	Minimum	Ideal Case	Maximum	Powder A	Powder B
Stability Index	0.65	1.00	1.20	1.03	1.52
Flow Rate Index	0.96	1.00	2.50	1.35	1.27
Cohesion (kPa)	0.11	Low	1.76	0.62	0.62
Wall Friction Angle (°)	10.40	Low	32.10	27.80	24.02

Table 2: Particle size data for Powder A and B is similar but a high SI correctly identifies the alternative powder as being unsuitable.

applied to differentiate powders that will print from those that will not and the parameters routinely measured now include:

- Particle size and size distribution (Dv10, Dv50 and Dv90)
- Particle morphology (shape)
- Stability index (SI)
- Flow rate index (FRI)
- Cohesion
- Wall friction angle
- Permeability
- Compressibility.

Tests are also carried out to assess binder compatibility.

Particle size and size distribution impact the flowability and packing behaviour of powders, as does particle shape; more regularly shaped particles are typically preferred for 3D printing because of their enhanced fluidity and packing efficiency. However, experience has shown that these parameters alone cannot identify powders that will perform acceptably in the company's printers. The remaining parameters are bulk powder properties – dynamic (SI and FRI), shear (cohesion and wall friction angle) and bulk (permeability and compressibility) – all now measured for each new powder using dynamic powder testing (Table 1 & 2).

Powder A and B have closely similar particle size distributions and scanning electron microscopy revealed comparable morphology (data not shown). In fact, the powders were only substantially differentiated in terms of SI, which at 1.52 was much higher for Powder B, outside the upper limit of 1.20. This figure suggests that the powder is physically unstable and in print runs the impact of this instability became clear. While Powder B initially performed well, the quality of printed parts gradually degraded over time to the extent that after 4–5 cycles it became impossible to print successfully. Further investigation ultimately attributed this behaviour to the presence of flaky particles becoming prone to interlocking and, by extension, poor flowability with re-use.

Experience at ExOne indicates that flowability data are critical in terms of defining the printability of powders and, as with conventional tableting, dynamic, shear and bulk properties are all relevant. Given the similarity of powder-liquid 3D-printing processes for pharmaceutical applications, it appears highly likely that this is a transferrable learning and that formulations for printing will also need to be specified with reference to all three types of properties.

CONCLUSION

3D printing holds considerable promise for the pharmaceutical industry. While early wins include the ability to deliver high dosages in rapidly dissolving tablets that ease the administration of drugs to patients facing difficulties with conventional oral solid dosage forms, the longer-term picture is transformative. Personalised drug products, containing a unique combination of active ingredients, printed to order at a unique dosage, in a local hospital or pharmacy, could be an achievable reality.

Those exploiting powder-based 3D printing technologies in other sectors have already discovered that such processes call for formulations with exemplary flowability and the measurement of dynamic powder properties has proven critical in differentiating powder that will print successfully. Such experience indicates that the application of effective bulk powder testing strategies will be essential to characterise pharmaceutical formulations for printing and realise the full potential of this exciting technology.

ABOUT THE COMPANY

Freeman Technology, a Micromeritics (Norcross, GA, US) company, specialises in systems for measuring the flow properties of powders and has >15 years' experience in powder characterisation. It invests significantly in R&D and applications development, and provides full support alongside its range of products.

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ABOUT THE AUTHOR

Jamie Clayton is Operations Director at Freeman Technology. He graduated from the University of Sheffield (UK) with a degree in Control Engineering and is responsible for all daily activities of the company, including overall management of the administration, production, R&D, sales and customer support teams. Mr Clayton also works with the company's clients to provide application-based support.

QUALI-V EXTRA DRY: A NOVEL CAPSULE FOR DELIVERING HYGROSCOPIC PHARMACEUTICAL DRUGS

In this article, Jose Luis Encinas, Engineering & Continuous Improvement Manager, and Susana Ecenarro, Director of Scientific Business Development, both of Qualicaps Europe, explore how the use of Quali-V® Extra Dry capsules can help improve product stability and, crucially, lead to efficiencies and savings in drug product manufacture.

A fundamental requirement in drug formulation is that the API remains stable under specific ICH environmental conditions and in the finished dosage form until the end of its shelf life to ensure efficacy and patient safety. The physical and chemical properties of pharmaceutical solids are critically dependent on the presence of water/moisture, e.g. during compaction, stability, storage, and processing into formulation and final product packaging. Many APIs, as well as excipients, are moisture sensitive and/or hygroscopic in nature and need to be protected as moisture can have a possible negative effect on their potency or strength, result in chemical degradation and/or polymorph forms, and could also potentially affect capsule characteristics.

Examples of current APIs in the market that are moisture-sensitive include pancreatin, omeprazole and lansoprazole (proton pump inhibitors), tiotropium bromide (inhalable powder), ranitidine, losartan, enalapril and dabigatran. Some common excipients that also fit into this category include PEG (low molecular weight), glycerine fatty acid esters or medium chain fatty acid triglycerides, sorbitol, maltodextrin, citric acid, microcrystalline cellulose (MCC), polyvinylpyrrolidone (PVP), croscarmellose sodium, sodium chloride, sodium sulphate, ammonium sulphate, amines and calcium chloride.

> "Particle aggregation due to moisture affects the emitted dose – that is, the powder released from the capsule and device – as well as the amount of drug that reaches and is deposited in the lungs."

Inhalable powders are also extremely sensitive to moisture, as aerosolisation properties and drug delivery performance can be greatly impacted by the amount of moisture present in the formulation. Particle aggregation due to moisture affects the emitted dose – that is, the powder released from the capsule and device – as well as the amount of drug that reaches and is deposited in the lungs.

The Quali-V® Extra Dry capsules developed by Qualicaps are specifically designed for use in administering these moisture-sensitive or hygroscopic formulations, both in solid oral and inhaled delivery forms, as the capsule moisture content has been reduced to 2-3.5%, from the standard HPMC capsule of 4-6%.

CHARACTERISTICS OF QUALI-V® EXTRA DRY

Quali-V® Extra Dry capsules are based on Qualicaps standard Quali-V® hydroxypropyl methylcellulose (HPMC) capsules, developed to respond to the growing market demand for moisture-sensitive and hygroscopic drug delivery. The primary difference is found in the

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manufacturing process. Traditional HPMC capsules are manufactured to obtain a final moisture content of 4-6% whereas, in order reduce this amount by almost half, the production process for Quali-V® Extra Dry was adapted to incorporate an extra drying phase – but without compromising the capsule's physical or mechanical properties.

Therefore, like Quali-V®, they are made from plant-based ingredients, preservative free, chemically inert and do not undergo crosslinking reactions.

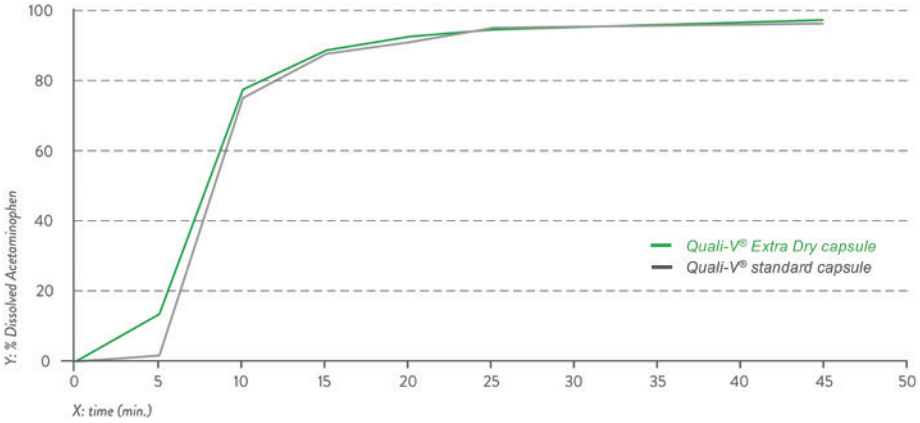


Figure 1: Dissolution profile for pH 1.2 capsule fill formulation – acetaminophen.

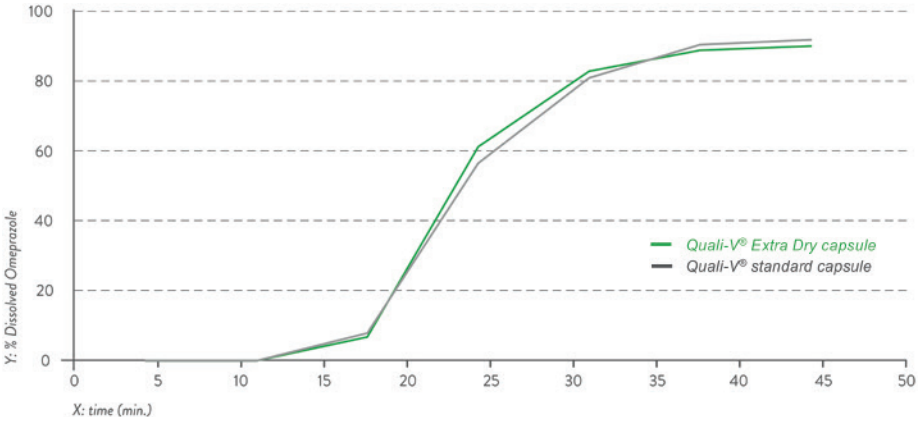


Figure 2: Dissolution profile for pH 6.8 capsule fill formulation – omeprazole pellets.

ENVIRONMENTAL CONDITIONS: 30° C/ 20% RH

	LOSS ON DRYING TEST *Moisture content (mean of 5 tests) (%)*	BRITTLENESS TEST *Broken capsules (%) (n=400 capsules)*
Batch E1703737	2.53	0
Batch E1702396	2.97	0
Batch E1610425	2.58	0

ENVIRONMENTAL CONDITIONS: 27° C/ 22% RH

	LOSS ON DRYING TEST *Moisture content (mean of 5 tests) (%)*	BRITTLENESS TEST *Broken capsules (%) (n=400 capsules)*
Batch E1703737	2.91	0
Batch E1702396	3.02	0

Figure 3: Capsule brittleness tests.

Quali-V® Extra Dry capsules are also equivalent in their dissolution profile to Quali-V®, which complies with the USP dissolution test requirements of >80% dissolved API at 45 minutes (Figures 1 and 2).

Quali-V® Extra Dry capsules maintain their physical robustness and present minimal brittleness when exposed to ambient temperature conditions and low relative humidity (RH: 22%), despite their reduced moisture content (Figure 3).

Quali-V® Extra Dry capsules preserve their moisture within the low range of 2-3.5% within ambient conditions from 15% RH to 25% RH – room conditions for low-moisture filling operations (Figure 4).

An important phase of the capsule development process is testing runability for commercial production scale. As such, Qualicaps has also tested Quali-V® Extra Dry capsules on several principal capsule high-speed filling machines – from manufacturers such as MG2, Bosch and IMA – in which they have demonstrated solid performance.

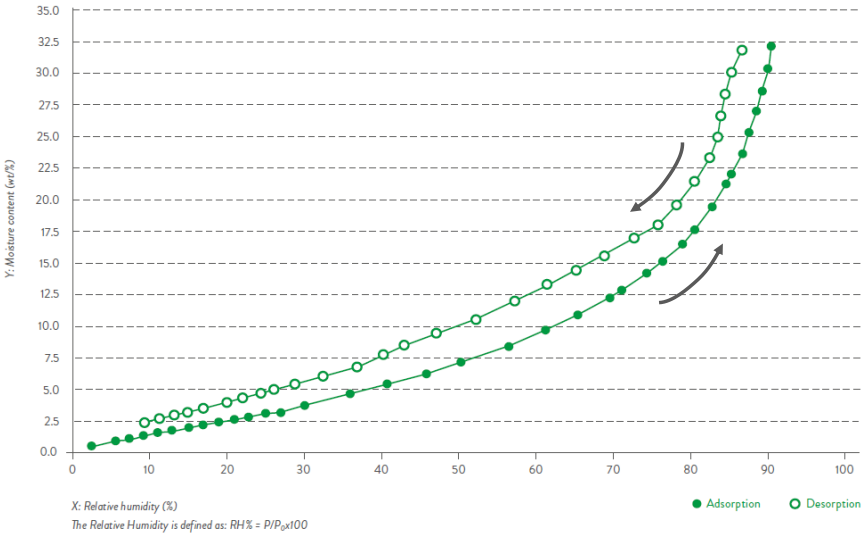
BENEFITS OF QUALI-V® EXTRA DRY IN THE FILLING PROCESS

The typical encapsulation process for moisture-sensitive drug products involves the feeding of the API formulation and empty capsules separately into the filling machine in a controlled environment. API moisture content, as well as filling room conditions, can be set precisely by the manufacturer but capsule moisture will be present throughout the process, during which some interaction with the API and excipients may occur.

Normally the final stage is drying the filled capsule – that is, moisture content is reduced from the final dosage form after the filling process takes place. As removing the moisture from the filled capsules may take up to several hours (some real examples include 6-8 hours, as well as 12-14 hours for different drug products), the drying step becomes a bottleneck in terms of timing within the drug manufacturing process – decreasing the overall yield.

As a result, moisture removal via drying the final dosage form has two principal disadvantages: firstly, there is a certain timeframe in which moisture from the capsule can interact with the moisture-sensitive drug formulation and, secondly, drying becomes a time-consuming part of the process with a low added value.

During the runability tests previously mentioned, Qualicaps simulated real



RH (%)	wt (%)
14,94	1,9771
16,90	2,1951
18,92	2,4111
20,95	2,6282
22,96	2,8464
24,91	3,067
26,74	3,286
30,11	3,7131
36,02	4,5543

The present data are obtained by means of a volumetric method as per USP41<1241>, EP9.0 2.9.39.

Figure 4: Water vapour absorption/desorption isotherm curve.

conditions of the filling process for moisture-sensitive drug products in order to study the behaviour and performance of Quali-V® Extra Dry capsules. By using these capsules (instead of traditional HPMC), the drying process can be avoided or at least significantly reduced. This means potential savings in total production time, as well as in equipment, production staff and utilities. The capsules also lead to the important benefit of limiting the exposure of the drug formulation (moisture-sensitive or hygroscopic API and/or excipients) to the moisture content present in the capsule.

PACKAGING, HANDLING AND STORAGE INDICATIONS

Produced under specific conditions, Quali-V® Extra Dry capsules are packaged in heat-sealed, moisture-proof aluminium liner bags to ensure the specified moisture content for 18 months – the shelf life of the empty capsules (a three-year long-term stability study is ongoing).

To prevent variability in shell moisture content, capsules should always be stored within the recommended temperature range – between 15°C and 30°C (59°F and 86°F). Maintaining the capsules within the liner bag (without perforations) safeguards them from both light degradation and moisture content changes, regardless of ambient humidity.

The conditions in areas where capsules could be exposed to air can affect the defined properties and/or machinability of the Quali-V® Extra Dry capsule. The ideal conditions for capsule filling (to maintain the moisture content of Quali-V® Extra Dry within the specified range of 2-3.5%) are established as follows:

- A temperature between 20°C and 30°C with a recommended set point of 25 ±2°C
- A relative humidity between 15% and 25% with a recommended set point of 20% ±2%.

The above requirement for handling during the filling and packaging process is the only one specific to Quali-V® Extra Dry.

CONCLUSION

Qualicaps developed the Quali-V® Extra Dry capsule to address the needs of the pharmaceutical industry as moisture-sensitive and hygroscopic drug formulations are increasing both in the marketplace and in R&D. While there is a current solution for this type of drug product, it depends on the manufacturing process itself, by introducing a drying stage after the capsule filling process. This unfortunately does not address the moisture content inherent in the capsule shell when it comes into contact with the fill – and can also negatively affect overall production yields.

Employing Quali-V® Extra Dry capsules instead of traditional HPMC capsules reduces both of these potential issues – potentially improving product stability as well as leading to efficiencies and savings in drug product manufacture.

ABOUT THE COMPANY

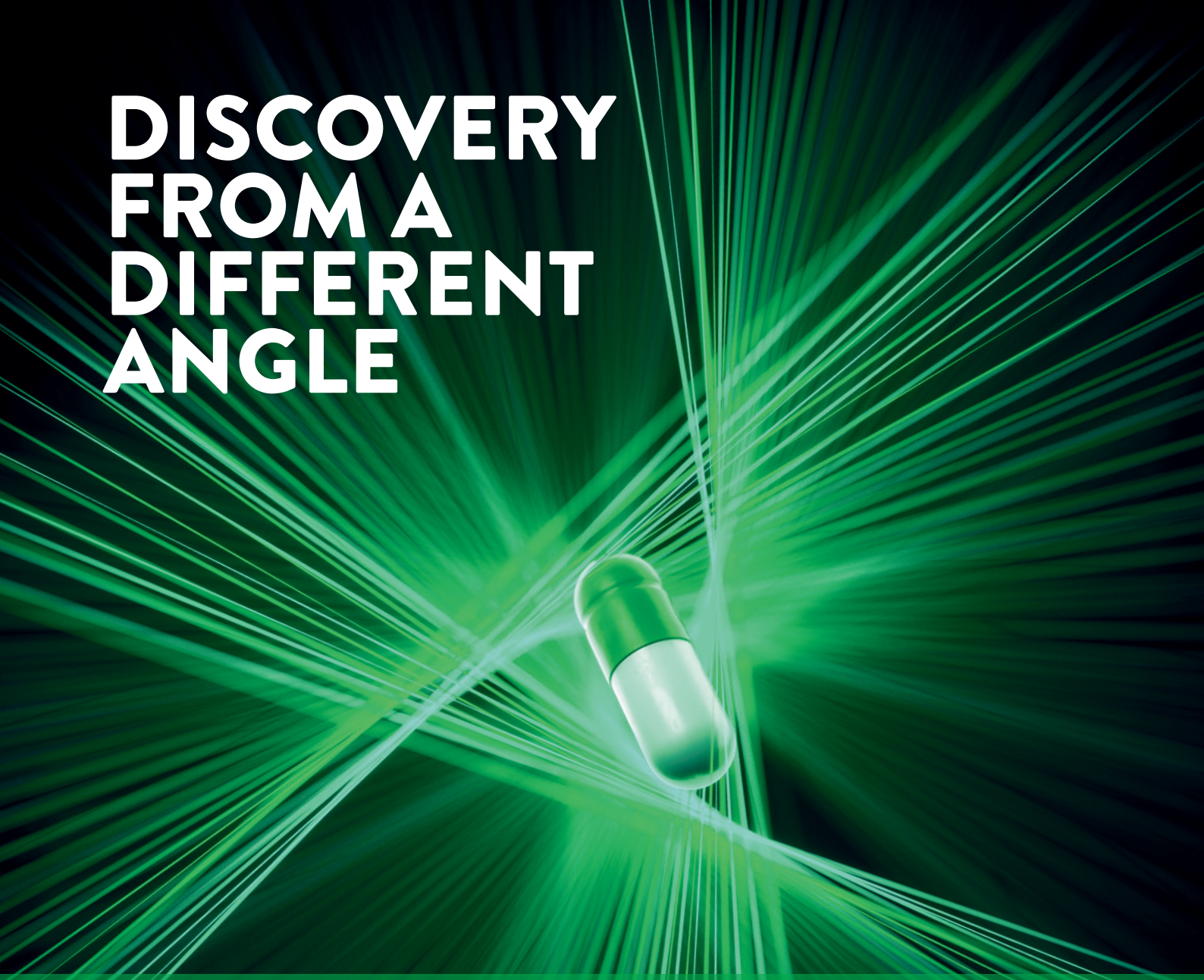
Qualicaps manufactures empty two-piece hard capsules for solid oral dosage forms and for use in dry powder inhalers, as well as a broad line of pharmaceutical processing equipment. The company's primary product portfolio in Europe includes gelatin and hypromellose capsules, though we often adapt these to specific requirements for customer drug developments.

ABOUT THE AUTHORS

Jose Luis Encinas is an Electronics Engineer with more than 18 years' experience in oral solid dosage form manufacturing technology. He has developed several roles and participated in various development projects for the last 15 years in Qualicaps and is currently Manager of Engineering and Continuous Improvement.

Susana Ecenarro is the Scientific Business Development Director of Qualicaps Europe. She holds an MBA and a bachelor's degree in pharmacy. Prior to Qualicaps, she worked for the German pharma company Schering AG for 18 years in different quality positions and covering several functions including analytical development, process validation, technology transfer and operation excellence projects, followed by five years of experience leading an analytical R&D unit of a Bayer Healthcare facility. Her main work mission in Qualicaps is to support R&D centres within the pharmaceutical industry in new drug developments by providing the scientific and technical expertise they might need, as well as promoting collaborations with European universities or third parties focusing on the application of state-of-the-art capsule technologies.

DISCOVERY FROM A DIFFERENT ANGLE



A NOVEL CAPSULE FOR DELIVERING HYGROSCOPIC PHARMACEUTICAL DRUGS

Qualicaps®, the company responsible for several milestones in the history of hard capsule development within the pharmaceutical industry, continues to innovate by presenting an extra dry cellulose capsule that will enable the development and production of moisture-sensitive and hygroscopic drugs.

Quali-V® Extra Dry, the cellulose capsule with an extremely low moisture content ideal for moisture-sensitive and hygroscopic pharmaceutical drugs.

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- *100% Vegetal origin*
- *Preservative free*
- *Standard HPMC Equivalent Dissolution Profile*
- *Minimal Brittleness*
- *Lower moisture content (2.0 - 3.5%)*

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INDUSTRIALISATION OF INHALATION PRODUCTS: OVERCOMING HURDLES AT COMMERCIAL SCALE

In this article, Robin Heath, Commercial Manager and Head of Supply Chain at Recipharm, discusses the typical challenges in scaling-up drug products from small-scale production to commercial manufacturing – and how these can be overcome.

Producing inhalation products at commercial scale has its own unique set of challenges compared with small-scale manufacturing. Manufacturing processes don't always perform in the same way at large scale and, as a result, the industrialisation step requires specialist knowledge of the potential hurdles that may need to be overcome.

> "It is critical to ensure a robust manufacturing strategy is in place prior to industrialisation."

OVERCOMING COMMON HURDLES IN COMMERCIAL-SCALE PRODUCTION

Successfully industrialising inhalation products requires several elements to be addressed, including the manufacturing strategy (scale, concept and layout), analytical release and stability testing, device component industrialisation and supply, process transfer and scale-up, regulatory considerations, supply chain management and product maintenance.

MANUFACTURING STRATEGY

It is critical to ensure a robust manufacturing strategy is in place prior to industrialisation. An understanding of the factors that influence the finished product batch size and manufacturing throughput is fundamental in determining capacity and unit price. The aim is to strike an optimum balance between the financial value of a single batch, the level of capital investment, the available capacity and the unit cost of the finished product.

For dry powder inhaler (DPI) products, batch size is usually governed by blend scale. There can, however, be other considerations such as the capacity of the filling and assembly equipment or its impact on the blend and finished product performance due to powder compaction or segregation. Invariably some form of conditioning may be required, typically a hold time for either the blend or filled product. The end-to-end manufacturing process is often separated into discrete stages. This allows confirmatory testing to occur before adding further value to a product. These requirements should be factored into the logistics of the manufacturing process.

The manufacturing strategy for metered dose inhaler (MDI) products (Figure 1) is usually more straightforward. The more universal design of an MDI means it is not usually necessary to commission a manufacturing operation around a bespoke product. The most common route is to use existing equipment. In these cases, batch size may be dictated by the pre-installed capacity of the chosen manufacturing facility.

When a bespoke delivery device is required (as is usually the case with DPIs), the pharma company often commissions a specialist equipment supplier to design suitable manufacturing/assembly equipment.

The level of automation and associated capital investment within the manufacturing

> "A compromise must be established between the relatively high initial investment associated with automation, versus a lower capital but higher ongoing labour cost solution."

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Figure 1: The manufacturing strategy for MDIs is usually more straightforward compared with DPIs.

process are also elements that need to be considered. A compromise must be established between the relatively high initial investment associated with automation, versus a lower capital but higher ongoing labour cost solution.

As well as financial considerations, there are also hurdles relating to ensuring that equipment design, layout of facilities and ways of working satisfy current cGMP requirements, as well as health and safety needs, including containment and emissions. Once a manufacturing strategy has been established, there will be capital investment and associated one-time costs required to industrialise the product. Cost and timescale certainty is usually critical and can only be achieved with proven skills and experience to support the specification, procurement and qualification of what is often bespoke or modified equipment and facilities.

SUPPLY CHAIN MANAGEMENT

In industrialising a new inhalation product, it needs to be ensured that the process can routinely produce a product that meets exacting regulatory standards, especially for delivered dose and aerodynamic particle size distribution. The selection and control of starting materials and manufacturing processes are critical in maintaining this capability.

One of the most significant challenges in the commercial production of inhalation products is supply chain management and ensuring a robust supply of the API. Particle sizing issues are common, so it is necessary to have an appropriate specification for the API. During the scale-up process, there is usually very little information to support that a company's chosen API supplier has the capability to continuously provide material against the correct specification. If an API doesn't continuously meet specification, there are going to be real problems with the finished product.

This challenge can also be extended to device components where there is the need for multiple components to be assembled. If the necessary specifications for these components are not set appropriately and/or are not routinely met, manufacturing problems will be encountered at some point. Using suppliers that can demonstrate capability at larger scale is fundamental. There is a need to understand the design space of the product throughout the development lifecycle and not limit this to just the formulation or the device.

Pharma companies need to understand what they require in terms of critical parameters for each material including the API, the device components and, to some extent, the excipients. The impact that particle size distribution can have on the final product's quality attributes demands that a robust definition of quality parameters is established. Design of experiments (DoE) offers the opportunity to look at the parameters and how they interact with each other. Parameters can be varied accordingly and optimised to routinely meet the desired product specification.

ANALYTICAL RELEASE AND STABILITY TESTING

Analytical testing relies upon consistent and robust specification testing – especially important for the key parameters of particle size distribution and delivered dose. There is a need to make sure that the API supplier has worked within their own design space and carried out their own DoE with the API material. Here we are looking for consistency of material. Particle size testing is a critical quality attribute for the finished product and, as the product moves into a commercial phase, there is a need to avoid having to undertake any redevelopment.

Analytical method transfer is especially important for MDIs and DPIs because of the challenging specifications required by regulatory authorities. This is usually the point at which the true variability within the method is understood and may be found to be unacceptable.

In addition, stability testing is fundamental to a product's overall strategy. It's about understanding what markets will be covered and the corresponding regulatory requirements for approval of a

> "When it comes to drug device combination products, the regulatory landscape can be more difficult to navigate as companies pick their way through the regulations and standards for varying authorities."

product in these regions. An understanding of the restrictions in different countries and markets must be established, as well as storage requirements that will need to be considered.

Stability study management also presents its own challenges due to the resource intensive nature of the testing and the tight product specifications which must be applied.

DEVICE COMPONENT INDUSTRIALISATION AND SUPPLY

Delivery devices are integral parts of MDI and DPI products. For new DPI products that involve a bespoke device, industrialisation is more complex due to the need to industrialise the device componentry at the same time as the manufacturing process. It is important to have a deep knowledge of the device design, often gained from single or low cavity injection mould tools and manual or semi-automated assembly processes. It is essential that critical features and dimensions within the device have been identified and tolerance analyses performed to ensure an appropriately specified device.

PROCESS TRANSFER AND SCALE-UP

Many commercial manufacturing challenges occur during the process transfer, scale-up and validation stages. As a product needs to comply with a specification routinely, it is essential to define the product's specifications based on manufacture and testing of an appropriate number of batches, using multiple lots of input materials and components. The manufacturer must understand the sources of variability within the manufacturing process that influence critical parameters such as assay, particle size distribution and dose. The application of statistical tools can identify, isolate and minimise these sources of variability during scale-up. The end result needs to be a process with a demonstrated capability to routinely meet the registered specifications.

REGULATORY CONSIDERATIONS

When it comes to drug device combination products, the regulatory landscape can be more difficult to navigate as companies pick their way through the regulations and standards for varying authorities. It's vital that companies stay up to date with continuously evolving regulatory requirements. Some products may take several years to reach the market and a lot can change in that time.

It is also vital that companies do not overlook fully understanding their commercial strategy. During the early stages of product development, customers have rarely given thought to a product's packaging, for example. With many wanting to package products as soon as a batch has been manufactured, this can mean frequent starting and stopping of the manufacturing/filling line to change the packaging format for different markets. In order to deliver an efficient operation, it is usually advisable to fill large batches of semi-finished product, then split these batches into multiple packed batches. Other important considerations here are to keep the product's packaging as simple as possible and consistent across multiple countries, where possible. This will not only help to simplify the manufacturing process but can also contribute considerably to reducing overall costs.

FINAL THOUGHT

A well thought through manufacturing strategy is key to overcoming hurdles during the scale-up and industrialisation process for any pharmaceutical product. This is especially true for inhalation products due to the integral nature of the formulation and delivery device.

A thorough strategy that is defined early on during the product's scale-up should minimise the need to repeat steps within the product development cycle and, just as importantly, should ensure that the manufacturing processes and analytical test methods are capable of complying with the registered specifications. This is critical to ensure the product can be routinely supplied on time and at the lowest possible cost.

ABOUT THE COMPANY

Recipharm is a contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. It operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US – and is continuing 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.

ABOUT THE AUTHOR

Robin Heath is the Commercial Manager and Head of Supply Chain for Recipharm's UK-based inhalation contract manufacturing facility. With 30 years of experience working in the pharma industry, Robin has a wealth of knowledge in product development and the industrialisation of several inhalation products. He has also had direct involvement with device suppliers to scale-up component moulding and device assembly processes.

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COMPACTION SIMULATION / INDUSTRIAL PRESS CORRELATION: TWO CASE STUDIES

In this article, Aline Moulin, PhD, Head of the New Product Introduction Department, and Lucile Kowalski, PhD, Pharmaceutical Development Project Manager, both of Skyepharma, examine two case studies comparing compaction simulation with industrial compression.

Compaction simulation has been of scientific interest since the 1970s, with a first compression simulator described in 1976.[1] The objective of compaction simulation is to be able to simulate industrial compression – that is, to be able to predict which parameters to apply on industrial equipment to obtain a tablet with the desired properties.

We have been involved in compaction simulation since 2016, with a STYL'One Evolution (Medelpharm, Beynost, France) compaction simulator. The choice of this equipment was driven by two key requirements. It had to be able to:

- Simulate industrial rotary presses
- Simulate complex compressions, such as multi-layer and tab-in-tab (also known as press coated tablets) which are the core Skyepharma development and industrialisation know-how.

Indeed, STYL'One Evolution has some characteristics that correspond well to our needs:

- It is equipped with two sensors on each punch thus allowing very accurate measurements of both tamping force and compression force in a very short time from 0 to 50 kN
- It simulates compression cycles of rotary industrial presses made possible by the fact that:
  - You will use the same punches and dies as the ones you use on your industrial equipment
  - The equipment mimics the kinetics of rotary presses, in terms of punches speed, penetration[2] and dwell time[3]
  - It also takes into account symmetric and non-symmetric punch penetration on your industrial equipment (Table 1).
- And finally, Medelpharm designed a specific feeding system for the introduction and centring of the core tablet during tab-in-tab compression.

> " The objective of compaction simulation is to be able to simulate industrial compression - that is, to be able to predict which parameters to apply on industrial equipment to obtain a tablet with the desired properties."

In the following paragraphs are two case studies of STYL'One / industrial equipment correlation established in our lab.

Press	Type	Compression Symmetry	Punch with Fixed Stroke
SVIAC PR51 CM3	Pilot multi-layer	Non-symmetrical	Upper punches
HATA HT AP LSU 3L	Industrial multi-layer	Non-symmetrical	Upper punches
FETTE P2100	Industrial multi-layer	Symmetrical or non-symmetrical	Upper punches in non-symmetrical mode
Kilian S 250 M	Industrial press coater	Non-symmetrical	Upper punches

Table 1: Different types of industrial presses of interest for our team.

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SVIAC

STYL'One

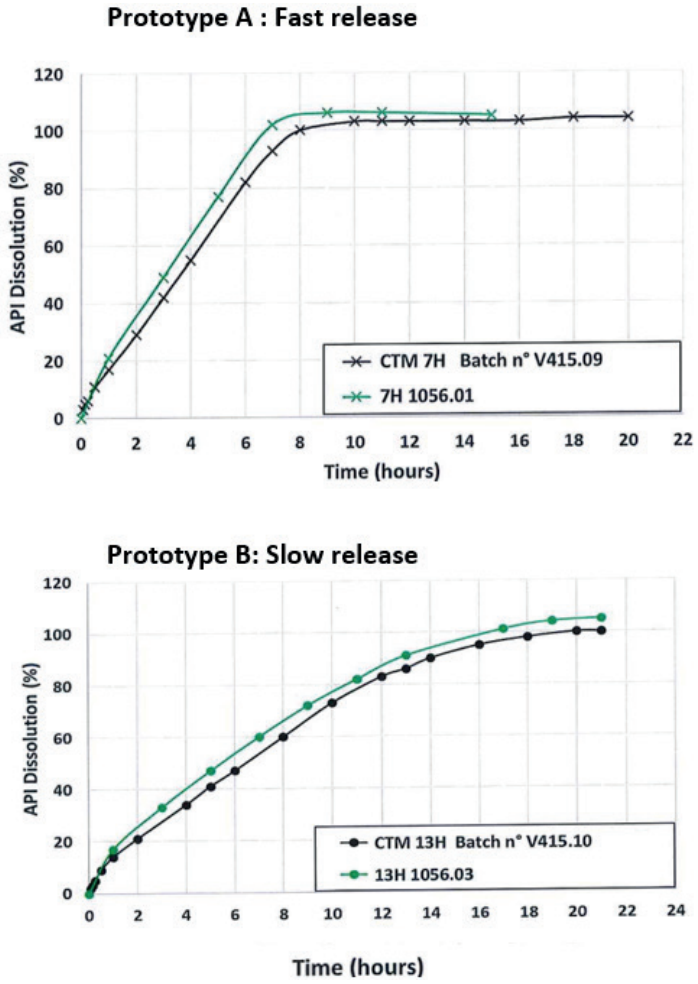

Figure 1: Dissolution profiles obtained for prototypes A and B manufactured with industrial equipment and with compaction simulator.

CASE STUDY 1: GEOMATRIX® MULTI-LAYER TABLET

Objective

The objective of this case study was to be able to replace the early-stage prototyping step we usually perform on industrial equipment (SVIAC PR51 CM3) by prototyping on the STYL'One Evolution.

Geomatrix® multi layer technology allows sustained release profiles to be achieved. Regulating and extending drug release is advantageous in many ways:[4,5]

- Reduced fluctuations of the blood concentration of the active ingredient might result in decreased occurrence and severity of adverse effects
- Prolonging of the plasma concentration of drugs with short half-life also means reduced administration frequency, and improved patient compliance
- Benefits mentioned above are particularly important not only for patients themselves but also for clinicians and pharmaceutical scientists.

Methodology

The methodology was to demonstrate correlation between STYL'One and SVIAC PR51 CM3 on prototypes – to demonstrate that similar dissolution profile performance could be obtained for batches manufactured with SVIAC and with STYL'One equipment.

Results & Discussion

Two different prototypes were tested: prototype A (fast-release prototype) and prototype B (slow-release prototype). For each of them, the dissolution profiles are displayed below (Figure 1), with two dissolution profiles for each of them:

- In black, the dissolution profile of the batch manufactured with the SVIAC PR51 CM3 equipment
- In green, the dissolution profile of the batch manufactured with the STYL'One Evolution compression simulator

We can observe that, for both prototypes, the black and green dissolution curves are similar (F2 > 50), thus demonstrating good correlation. Encouraged by these good results obtained on multi-layer tablets, we looked at even more complex oral solid dosage forms, i.e. press-coated tablets.

> "The most critical facet of a pulsatile release formulation is lag time, which can be engineered through different formulation strategies such as film coating or compression coating."

CASE STUDY 2: GEOCLOCK® TAB-IN-TAB/PRESS-COATED TABLET

Objective

This case study is about a tab-in-tab product, using Geoclock® technology, developed as a time-controlled pulsatile release formulation.[6,7,8]

Chronological disorders exhibit diurnal variations in their amplitudes owing to the circadian rhythm of the body (the body clock). Various chronological disorders – such as bronchial asthma, rheumatoid arthritis, variant/Prinzmental's angina and hypertension – exhibit peak disturbance in the early morning when patients are asleep. Conventionally, such early-morning attacks are treated with bedtime administration of medicines in the form of either immediate release or extended release formulations. In such cases, although effect is needed only in the early morning, the drug is continuously released throughout the night; entailing higher doses to extend its effect up to the next morning, with some risks of side effects.

One alternative approach is the pulsatile drug delivery system that can restrict the release for a predetermined period and subsequently provide burst drug release to exhibit peak effect in the early morning. The most critical facet of a pulsatile release formulation is the lag time which can be engineered through different formulation strategies such as film coating or compression coating.

Administration of the proposed formulation is made at bedtime and will release the drug only after midnight to provide the effect in the early morning.

The product of our case study presents a lag time, with a very narrow performance window:

- Sufficient lag time is needed to obtain the delayed release performance for middle-of-the-night delivery
- A too long lag time is to be avoided because of loss of bioavailability (API less absorbed in the colon).

Our objective was to demonstrate correlation between KILIAN S 250 M and STYL'One Evolution on this specific process.

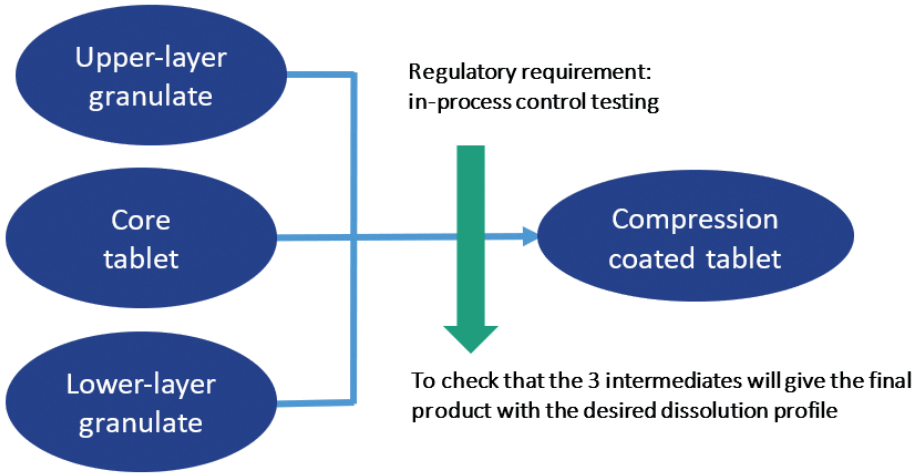

Figure 2: General scheme of the manufacturing process.

Methodology

Figure 2 presents a high-level scheme of the process: manufacturing of the core tablet, of the upper-layer granulate and the lower-layer granulate, and final compression of the press-coated tablet. Given the very narrow performance window of this product, a press setting is performed to determine at which pressure the three intermediates will give the final product with the desired dissolution profile.

This setting is currently performed on an industrial KILIAN S 250 M press, and we wanted to see if it was possible to perform it on the STYL'One Evolution compression simulator. So a preliminary study was performed to compare lag-time dissolution performance between batches manufactured on both types of equipment.

Results & Discussion

The comparison was performed with three different independent batches. For each of them, the setting was performed with Kilian equipment and with STYL'One Evolution equipment. Three different compression forces were tested – A, B and C – to determine if the resulting lag time was compliant with specifications.

The setting performed on STYL'One Evolution gave the same results as the one performed with KILIAN (Figure 3). That means the setting performed on STYL'One Evolution allows selection of compression pressure that, once applied on Killian S250, will give drug product with compliant lag time. Based on correlation observed in this case study, definition of the press-coating compression force required for industrial tablet press could be carried out on the STYL'One with minimal waste of resources.

	Mean Lag time vs compliance to specifications (dissolution on 6 vessels)			Selected Compression force to provide proper lagtime
	Compression Force A	Compression Force B	Compression Force C	
Batch 1 (Kilian S250M)				Compression Force B
Batch 1' (Styl'One Evolution)				Compression Force B
Batch 2 (Kilian S250M)				Compression Force C
Batch 2' (Styl'One Evolution)				Compression Force C
Batch 3 (Kilian S250M)				Compression Force C
Batch 3' (Styl'One Evolution)				Compression Force C

Not compliant | Compliant

Figure 3: Comparison of the results obtained with Kilian and with STYL'One Evolution.

CONCLUSION

Good correlations were established between industrial equipment and the STYL'One compaction simulator, on two different examples: multi-layer tablet and compression-coated tablet. Based on these results, we can move forward by using the compaction simulator at different stages all along the pharma development of a new project – early stage, scale-up, quality by design with design-of-experiment matrices performed at small scales, and even in-process control during commercial manufacturing.

ABOUT THE COMPANY

Skyepharma provides solutions bringing value to its clients at any stage of a product development lifecycle, from early-stage development up to commercial manufacturing and packaging activities. Skyepharma's value proposition includes services tailored to clients' requirements, supporting them up to market for their solid dosage form projects.

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ABOUT THE AUTHORS

Aline Moulin graduated from the National Graduate Chemistry School of Montpellier (France) and received her MSc in Biomolecular Chemistry from the University of Montpellier in 2004. She then achieved her PhD at the Institut des Biomolécules Max Mousseron in Montpellier. She was appointed Medicinal Chemistry Research Scientist in 2007 at Sanofi Research Center (Vitry sur Seine, France). She joined the Flamel Technologies (now Avadel Pharmaceuticals, Venissieux, France) R&D team in 2009 to work on the design, development and industrialisation of drug delivery systems. In 2018, she joined Skyepharma as Senior Project Manager and was appointed Head of the New Product Introduction Department in 2019.

Lucile Kowalski was awarded by the University of Pharmacy of Grenoble (France) in 2017 and received her MSc in Formulation and Industrial Chemistry from the University of Lyon (France) in 2017. Then she achieved her PharmD in 2019 on compaction simulation. During her years of study, she worked as an intern at Creathes (Hericourt, France) on micro-organism encapsulation and at Molecular Pharmacochemistry Department (UMR 5063) on encapsulation for ophthalmic route. She joined Skyepharma in 2016 as an apprentice and was appointed Project Manager in 2017.

PERSONALISING DRUG PRODUCTS USING 3D PRINTING

The use of 3D-printing technology to create personalised drug therapies is providing some exciting opportunities for improving patient care. Sarah Trenfield, PhD, Director of Innovation and Abdul Basit, PhD, FabRx Co-Founder and Director look at the potential applications in fields such as multiple drug therapy and paediatric/geriatric care and explore how FabRx's 3D-printing system can produce a range of different formulations to suit a variety of situations.

Consumers are increasingly interested in shaping the services and products they receive. Recent research has highlighted that more than 50% of consumers express an interest in purchasing customised products or services. This demand will require adaptation by multiple industries,[1] including the pharmaceutical sector. Since the Precision Medicine's Initiative was released in the US in 2015, pharmaceutical research has been pursuing the development of more tailored treatments in an attempt to make medicines safer and more effective. This is critical for complex medication regimes, e.g. multiple dose changes and those with a narrow therapeutic index (i.e. where the level between the therapeutic and toxic is very narrow).

> "Due to the highly flexible nature of the 3D-printing process, the applications of this technology are extensive."

However, the main manufacturing methods for oral dosage forms (tableting and encapsulation) are not able to meet the need for this type of therapy – they were invented over 200 years ago, when cheap, high-volume processes were prioritised over smaller scale, personalised treatments.[2] We therefore need to look at new technologies that can provide bespoke tailoring of drug products to suit the individual needs of each patient.[3] One such possible technology is three-dimensional (3D) printing. 3D printing is an additive manufacturing process where dosage forms are designed using digital software and sent to a 3D printer to enable on-demand, layer-by-layer production of printlets (3D printed tablets).

Since 2014, FabRx has been driving the use of 3D printing in pharmaceuticals by developing a wide range of 3D-printing technologies and formulations suitable for personalised oral dosage form and medical device production. So far, FabRx processes have produced printlets for multiple drugs, flexible dosages, tailored aesthetics (shape, size, flavour and colour) and drug release, giving patients a truly personalised treatment approach. In 2018, FabRx was awarded a grant of nearly £1 million from the UK government's innovation agency, Innovate UK (Swindon, UK), to develop the world's first regulatory-approved personalised medicine 3D printer, enabling it to conduct the first clinical study in the world using 3D-printed medicines in paediatrics.[4]

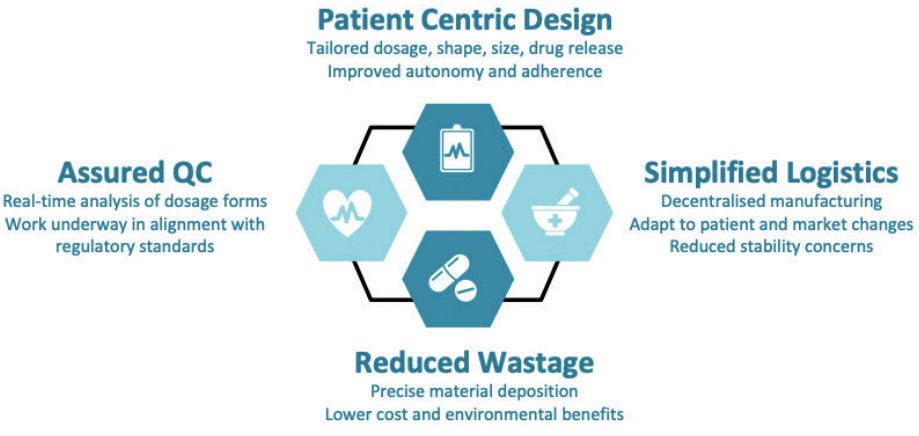

Figure 1: Key benefits of FabRx's 3D-printing technology for pharmaceuticals.

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Advantages

The key benefits of FabRx's proprietary formulations and 3D-printing processes (Figure 1) include:

- Patient-centric design: The pharmacist can input parameters such as the dosage, shape, size and type of drug release (immediate through to controlled release) to create a tailored drug product, which maximises medication adherence, clinical efficacy and safety.
- Simplified logistics: The 3D-printing systems are both compact and portable, meaning pharmaceuticals can be manufactured on-demand in decentralised locations. Systems can be integrated into clinical settings e.g. hospital, community pharmacies and out-patient clinics, or within remote areas such as disaster zones or even space. On-demand production makes it easier to adapt to changes in patient or market needs, and can also highly benefit medicines that have poor stability or those that require costly cold-chain storage.
- Reduced wastage: FabRx's 3D printers are able to deposit the exact amount of drug product material. This reduces material waste, which is a common problem in pharmaceutical manufacture. It could also reduce costs for preclinical and clinical studies conducted with highly expensive drugs, e.g. in orphan diseases, as well as have environmental benefits.

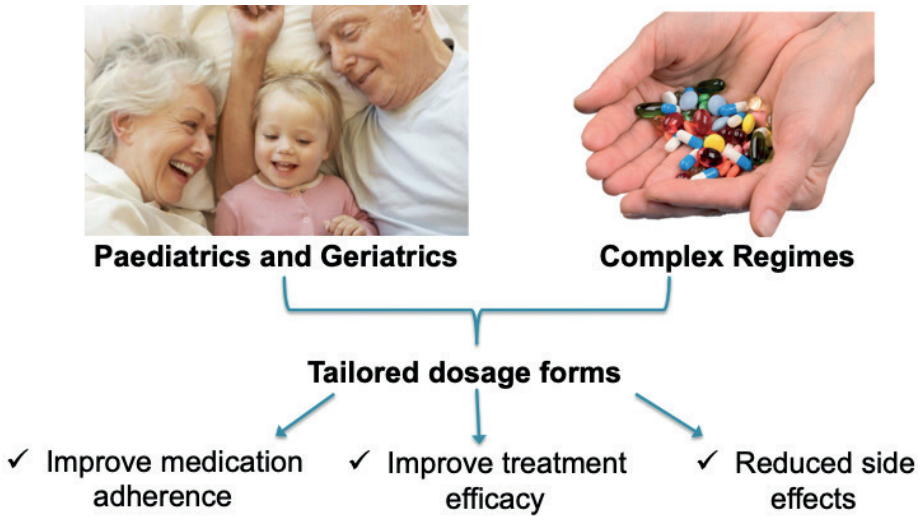


Figure 2: Main applications of 3D-printed medicines.

- Assured Quality Control: FabRx's pharmaceutical systems are being developed in close communication with regulatory agencies, e.g. the UK MHRA, US FDA and EU EMA, and hospital end-users to create a system that is fit-for-purpose.[5] The team are integrating real-time quality control measures to ensure product efficacy and safety.[6]

Using FabRx's 3D-printing process could generate increased revenue for pharmaceutical companies through increased medication adherence, improved efficacy and safety profiles, as well as increased product margins via premium pricing.

Figure 3: FabRx's semi-solid extrusion 3D-printing process to create chewable printlets – ideal for treating children.

APPLICATIONS OF 3D PRINTING MEDICINES

Due to the highly flexible nature of the 3D-printing process, the applications of this technology are extensive. Although it is unlikely to match the economies of scale for mass-manufactured drug products, 3D printing is well suited to more niche conditions and patient populations, for which current treatment pathways are substandard.

Dose Changes and Geriatric/Paediatric Patients

One such application is for drugs that require frequent dose changes e.g., those with a narrow therapeutic index, or in geriatric and paediatric populations, where dosing requirements can vary markedly (Figure 2). Patients often manually crush or split tablets to achieve the correct dose, which has inherent safety risks. FabRx has therefore focused on developing 3D printers as automatic compounding systems to get the correct dosage. Using a process called semi-solid extrusion, FabRx can produce chewable tablets with precise dosages, shapes and flavours, which can improve medication adherence and acceptability particularly in paediatrics (Figure 3). Indeed, it could be possible for the patient to become involved with the medicine design process, which facilitates patient autonomy.

Clinical Trials

In 2019, FabRx invented a revolutionary 3D-printing system for the production of pharmaceuticals. The system, known as direct powder extrusion, enables the production of drug products in a single-step process directly from powdered

"FabRx has created dosage forms impossible to produce using conventional methods."

materials, avoiding the lengthy methods usually required to produce 3D-printer filament feedstock.[7] This technology enables flexible and tailored dosing with minimal development times, which is showing promise in the field of preclinical studies and early phase clinical trials.

Multiple Drugs

Using 3D printing, FabRx has created dosage forms impossible to produce using conventional methods (Figure 4). In one study, the FabRx team 3D-printed pellets (termed miniprintlets) containing two drugs for tailored analgesic therapy (Table 1).[8]

3D printing could also be useful for those on complex medication regimes. Polypharmacy (the administration of more than one medicine) is a common practice for elderly patients. However, this can cause confusion and difficulty managing the medication. FabRx 3D printers have instead been used to print multiple drugs into the same dosage form to create 3D-printed polypills (aka polyprintlets). As an example, six different drugs were printed in a multi-layered configuration, reducing the number of tablets to just one (Table 1).[9] Furthermore, dosage forms with unique and tailored drug release profiles, ranging from rapidly disintegrating dosage forms through to controlled release, have also been produced, simply by altering the printlet geometry or excipient composition.[10,11]

Figure 4: Printlets created using FabRx's pharmaceutical 3D printer.

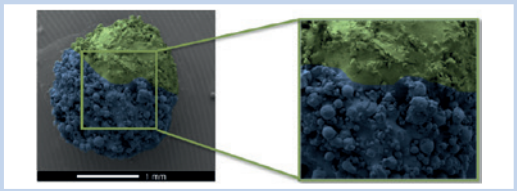
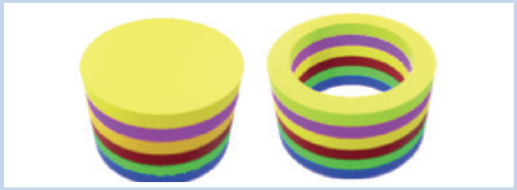
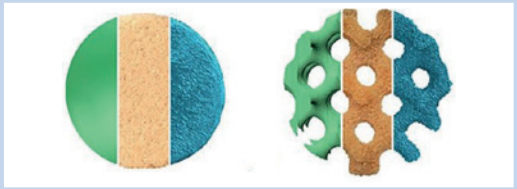
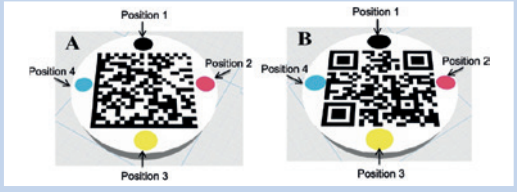
Phase	Image	Reference
3D printed pellets containing paracetamol and ibuprofen		8
Six layered polypill in cylindrical and ring-shape formations		9
3D printed tablets of cylindrical and novel geometric lattice shapes		10,11
Novel anti-counterfeit measure using QR codes and smart material inks		12

Table 1: Novel applications of 3D printing using FabRx technologies.

Global Health

The benefits of 3D printing could also have a wide-reaching impact on global health, tackling major challenges such as the counterfeiting of medicines. It is estimated that 10.5% of low- and middle-income countries are affected by substandard or falsified medicines, costing an estimated US$30.5 billion (£24 billion) annually. To overcome this, the FabRx team developed a unique track-and-trace and anti-counterfeit method, whereby QR codes and smart material inks were printed directly on the surface of drug-loaded tablets to ensure product authenticity (Table 1).[12]

CLINICAL TRIALS

As a world first, FabRx's personalised medicine 3D printer was integrated into a hospital setting to treat children (aged 3–16 years) with maple syrup urine disease (MSUD).[13] The first-line therapy for MSUD involves dietary leucine restriction and the oral supplementation of isoleucine and valine. The dose administered to patients requires strict tailoring according to age, weight and blood levels. In current clinical practice, however, practitioners are required to prepare extemporaneous formulations due to the lack of suitable oral treatments for MSUD.

To overcome these challenges, FabRx's 3D printer was integrated into the Pharmacy Department of the Clinic University Hospital in Santiago de Compostela, Spain, to produce chewable tablets containing personalised dosages of isoleucine.[14] A variety of dosages, colours and flavours were created, which were evaluated for patient acceptability and therapy control. The researchers found that 3D printing enabled a tighter control over target blood concentrations compared with the standard therapy (capsules), and that the flavours and colours of the 3D printed dosage forms were well accepted amongst all patients.

This study was a significant milestone in 3D-printing history and demonstrated the true benefits of such technology.

CONCLUSION

It is becoming clear that 3D printing has a promising role in the future of oral drug delivery, transforming medicine production away from mass manufacture towards highly tailored dosage forms on demand. With the adoption of non-invasive diagnostics or drug monitoring strategies, 3D printing could provide a novel, digitised platform to create tailored medicines in response to changes in clinical needs. FabRx is providing a flexible dosage form production system using 3D printing to realise the potential of this technology in pharmaceuticals, making treatments safer and more effective for patients.

ABOUT THE COMPANY

FabRx was established in 2014 by leading academics from University College London (UCL), specialising in the development of 3D-printing technology for medicines and medical devices. Since its initiation, FabRx has developed more than seven different types of pharmaceutical 3D printers and in 2017 received the TCT Best Start Up Award. In 2018, FabRx was awarded a grant totalling nearly £1 million from Innovate UK to develop the world's first personalised medicine 3D printer, and conducted a world-first clinical study using 3D-printed medicines in paediatrics.

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ABOUT THE AUTHORS

Sarah Trenfield is the Director of Innovation at FabRx, specialising in the development of 3D-printed medicines and medical devices. She qualified with a first class Pharmacy degree from Cardiff University in 2015 and undertook her pre-registration year at MSD. In 2016, Dr Trenfield successfully registered as a Pharmacist and began studying for her PhD at UCL on 3D-printed medicines funded by the EPSRC (EP/L01646X). Since then, she has published more than 17 articles and book chapters on the topic, presented at national and international conferences and received prestigious awards from the AAPS, Pfizer and UCL on her research.

Professor Abdul Basit is the Formulation Director at FabRx and he holds the position of Professor of Pharmaceutics at the UCL School of Pharmacy. Dr Basit's research sits at the interface between pharmaceutical science and gastro-enterology, forging links between basic science and clinical outcomes. He is an international authority on oral drug delivery and absorption, and has published over 300 papers, book chapters, abstracts and patents. Dr Basit was the recipient of several awards including the Young Investigator Award from the AAPS and is the only non-North American scientist to receive this award.

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BOB TILLING, KALLIK

Bob Tilling, Business Development Manager at Kallik, has spent most of the last 20 years working with companies to help them identify and implement solutions to overcome challenges in the factory-based labelling of pharmaceuticals and medical devices. His experience is gained from having first-hand experience with over 80 company-wide factory labelling implementations with customers located across the EU and US. The focus of his effort has been reducing factory labelling errors at print time to reduce risks of non-compliance, achieved by reducing operator input and automating the print processes wherever possible.

In this interview, Mr Tilling shares his insights on best practice for factory labelling.

Q Firstly, can we define what we mean by "factory labelling", and the labels this applies to?

A "Factory labelling" or "factory print" applies to all forms of printed label. Considering labelling for drug delivery devices, the device itself needs to have a label attached to it. The device packaging whether it be some sort of pouch, polythene bag or cardboard carton will also need labelling as will the shipper. Whilst these labels would be similar, the quantities are usually different so it's imperative that the relationship between the devices, their associate labelling and types of packaging are correctly maintained to avoid incorrect quantities in the box being shipped to, for example, the hospital. This could otherwise result in serious consequences for the patient downstream due to operations being disrupted resulting from unforeseen stock-outs.

Q What key criteria need to be addressed as part of a factory labelling solution?

A Firstly, factory labelling represents a much bigger task than most realise. If you look at the US FDA requirements, we know that labelling encompasses IFUs, booklets, promotional materials as well as the label. We also know that from their reports that somewhere between 50 and 75% of errors that the FDA highlight are based on some sort of labelling error. These errors also get reported on the Wikipedia pages of medical device and pharma companies so these issues can become highly transparent and potentially not only affect an organisation's share price but also public confidence.

Q Before getting into the specifics of factory labelling, can you share some insight of what's involved in either creating a new label or modifying an existing one?

A Changes or new label artworks for new products need to be circulated around multiple stakeholders for review and approval before reaching the print stage. This group includes regulatory, marketing, brand management, production and supply chain teams. Once that label's artwork has been approved, the labels will then be test printed as part of the approval process. Where quality control is paramount, these labels will be test printed on the actual printer with the correct label stock with a sample of the variable data that matches real-life production. The approval process for a new bath of labels can take anything from 2-6 months.

> "Between 50 and 75% of errors that the FDA highlight are based on some sort of labelling error. These errors also get reported on the Wikipedia pages of medical device and pharma companies so these issues can become highly transparent and potentially not only affect an organisation's share price but also public confidence."

Q What are the main reasons behind this being a lengthy process?

A It comes down to time taken to review changes and make decisions in the context of being personally accountable – even more so these days with electronic signatures. Often requirements are different in each country involving the need for local translations. The overall process from identifying new requirements through to running localised test prints in the factory consumes a huge amount of valuable time and resources to ensure the final label layouts and content are correct before going into production.

Q This all sounds fairly straightforward, so what tends to go wrong?

A Problems can arise with the disconnect that exists between the aforementioned process and the print operator in the factory responsible for making sure the right labels get printed for the right products. The first challenge for operators is to identify what products they have in front of them. Even if they are skilled, experienced and recognise the different types of products they need to

"If connected to the factory print solution, the ERP system could automatically tell the printer to print the label with the correct size on it. All the operator then needs to do is to apply the correctly printed label to the correct product."

print labels for, they then need to identify the correct label type. Sometimes there is some form of look-up they can perform on a local PC to help, but often the operator will need to scroll through a long list of labels to try to recognise the label needed at that particular time, whether this be the inner label, outer label, box label, carton label or patient label. The operator has to make this decision and sometimes this decision is wrong.

Q What's the impact of making the wrong decision at this point in the process?

A A product could be mislabelled, a product could carry the wrong information, a label could be missing out of the required set or possibly a combination of these things might occur. This could result in the product being misused, patient specific pharmaceutical products could even carry the wrong dosage, potentially leading to patient injury or even death.

Having gone to all the trouble of getting everything right upstream, organisations should not then rely on one individual in a factory to make a whole host of selections to attempt to get the right label on the right product. In most people's minds, there would be little point in going through an extensive upstream review and approval process and then leave it to a relatively low skilled individual in a remote factory to make a series of complex decisions to attempt to place the right labels on the right products.

Also, it's not just product types that can change, it's also the number of variants in size for a single product - for example selecting the correct label for a specific size and dose of transdermal patch. With disconnected factory print solutions, it's left to the operator to select the label specifying the correct size, introducing opportunities for mistakes. It makes no sense to leave this decision to the print operator when the actual size of the product is known to the organisation's enterprise resource planning (ERP) system. If connected to the factory print solution, the ERP system could automatically tell the printer to print the label with the correct size on it. All the operator then needs to do is to apply the correctly printed label to the correct product.

Q This seems a logical approach, so why doesn't this happen today?

A Organisations either take one of two approaches. Either they adopt a company-wide global labelling and artwork management solution or they tend to have local instances of software installed solely for printing the label in the factory. It's easy to install a factory label printing system with no connection to anything else and feed a piece of paper to it. It's also easy to lean on somebody who's got some experience and seems to know what they're doing. 99% of the time it works fine as a low cost - low tech solution, but it's the impact of the 1% when it goes wrong that causes the problem. The 1% chance of a labelling error on a high-street product isn't going to be the end of the world, but in the context of pharmaceutical products, if the error leads to adverse effect on a patient, then the consequences are severe.

Again this can apply to variable data. Why ask an operator to type in a batch number or LOT number? What if they type it incorrectly? What if they choose the wrong one? Similarly, why let an operator type in an expiry date? Calculating expiry dates with connected systems is simple and takes away any margin for error. Similarly this can apply to patient-specific variable data. Patient specific products can require up to 50 digits to be typed in by the print operator to generate the correct label. If any one of these is wrong, the wrong information goes on the label and the label can be misleading.

Q Why aren't these localised print solutions connected to upstream production systems as you suggest? Surely it can't be that difficult to do?

A It isn't that difficult to do, but it's perceived to be more troublesome to do than have people double and triple checking printed labels both before the label reaches the factory and after the label has been printed and applied in the factory. It's often the case that the amount of time an organisation spends checking and rechecking the label at the various stages of design and print remains invisible to executive management. It's not until this is brought to light that there is a realisation that there is a waste of valuable resources that could otherwise be better utilised increasing production and reducing downtime.

Q In your view, what would be the ideal solution to overcome the problems you've talked about?

A The ideal solution is automation on the factory floor where the only choice the operator makes is which job will I do next? From then on, they are automatically given the right label, they're automatically given the variable batch information and they're told what to do with that label and where to put it. If the label is part of a set, the correct quantities of labels are all printed at the same time. Even where a selection of the printed labels are applied further downstream, it is still better to print all the labels at the same time ready to be applied when the products are placed in the final carton. In this way, you're not asking three separate operators to make a decision, it's all done by one operator.

The other thing that often goes wrong is that the operator will send the print job to the wrong printer or the wrong type of printer, resulting in misprints or the barcode not printing properly because the printer may not be capable of printing it to the required size or scale. The operator may change the print speed or the temperature settings in the printer, leading to issues such as dosage symbols being misread or not recognised properly, or part of the label can be missing due to wrong paper stock being used to print a certain type of label.

With a connected solution, the system knows what stock you used to run "Job A", if you move to "Job B", the system knows you need to change the label stock. The system can then tell the operator to change the stock rather than relying on him or her to select the correct stock?

Q It sounds like you're suggesting that holding the intelligence relating to the different types of printers and printer

> "Factory print takes place within a carefully controlled environment. It's also the end part of a very long, highly regulated process. There's little sense in allowing uncontrolled choice and flexibility at the end if you tightly control everything up to that point."

capabilities within centralised solution makes it easier to route the right jobs to the right printers, reducing the risk of errors.

A Exactly that. Such a factory print system will capture where the printers are physically, what ports they're on and what types of printers they are so the system has a global view of all available printing resources. At the same time, because you're managing all labelling content centrally, you know the label size and the print quality requirements to enable the correct printer and printer settings to be selected for each and every label. You'll also know that when the labels to be printed in a subsequent print job are of a different size, a message automatically gets sent to the operator to change the label stock. This approach takes away the risk of operator errors, reduces wastage and ensures the right quality and quantity of labels are printed and are right first time.

Q Are there any other insights you'd like to share about deploying a factory print solution?

A Factory print takes place within a carefully controlled environment. It's also the end part of a very long, highly regulated process. There's little sense in allowing uncontrolled choice and flexibility at the end if you tightly control everything up to that point. So unless you tighten the process up at the final print stage, there's really little point in running a set of tightly controlled processes further upstream.

At its core, a better approach allows the management of all labelling content in one central platform that provides all stakeholders with full end-to-end visibility of the label design and print process. Any discrepancies between label design and print capabilities can then be surfaced much earlier in the process, further reducing the risk of downstream stock-outs.

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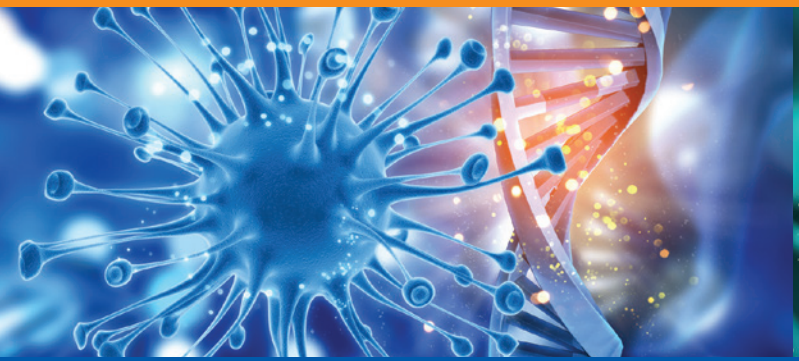

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AUTOMATING PREVIOUSLY IMPOSSIBLE MANUAL INSPECTIONS USING MACHINE LEARNING & CONCURRENT VALIDATION

In this article, Steve Wardell, Director, Imaging, and Catherine Thacker, Director, Pre-Automation Solutions, both of ATS Automation, explore how machine learning technology is enabling the automation of challenging, or previously impossible, manual inspections.

Every manufacturing process has one – the difficult manual visual inspection process that seemingly cannot be replaced with an automated inspection process. The two major hurdles are finding a technical solution that duplicates what human inspectors accomplish naturally – and proving the equivalency of machine-based inspection with human inspection.

Advancements in the field of machine learning now make the automation of many of these challenging inspections possible. ATS Automation and its vision group have continued to develop inspection capabilities leveraging machine learning techniques and are now enabling the move away from manual processing toward automated processing.

THE CRITICALITY AND SENSITIVITY OF RELIABLE VISUAL INSPECTION

Visual inspection plays a critical role in assuring the quality and repeatability of a manufactured product. Whether we inspect to make sure the product is within specification or we inspect to verify compliance with industry standards, these inspections are a necessary part of any manufacturing process (see Table 1).

The nature, complexity and criticality of visual inspections influence the inspection approach, namely manual, automated or a combination. The scale can range anywhere from periodic sampling, or auditing, to 100%, or complete, inspection of all parts produced. Where there are multiple process steps, there can be in-process visual inspections to flag defects early and avoid subsequent value-add processing. The reliance on operators for these inspections comes with a high price tag.

But how do we move toward automated inspection? In applications where a human inspector examines a component with their eyes and checks for defects, an analogous automated system has to duplicate not only the gathering of the image of the part but

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Inspection Category	Examples
Finished product quality checks	Cosmetic defects, colour, fill level, seal quality (contamination, homogeneity), particulate
In-process quality checks	Presence/absence, orientation or position, colour, glue pattern
Counting and verification of counts	Reconciliation of components, e.g. labels, plastic parts, verification of reject action success
Regulatory requirements and compliance	Batch number and expiration dating information, serialisation
Customer assurance	Final functional / performance checks
Safety requirements	Package integrity, leak detection
Process improvement and diagnostics	Machine monitoring, operator assistance and supervision
Metrology and measurements	Insertion depth, placement position accuracy, volume dispense, seal width

Table 1: Typical inspection categories in manufacturing.

> "In this industry, all automated systems need to demonstrate that they are at least as capable as a standard trained operator under well-defined conditions."

also the analysis of that image to decide whether or not there are defects present. In some situations, this can be very difficult due to the nature of the defects and/or the parts themselves (Figure 1).

A good example is the manufacture of certain types of pharmacological products. Within the pharma industry, the assurance that the sellable product (medicines, tablets, vaccines, etc.) is without defects is of paramount importance. Therefore, manufacturers put a strong emphasis on the deployment of inspection systems throughout their manufacturing process. Historically, many of these inspections have been manual because the automated solutions' reliability was unable to match that of the operators trained for the job – or because a strong validation case could not be made. In this industry, all automated systems need to demonstrate that they are at least as capable as a standard trained operator under well-defined conditions.

Human inspectors have the innate ability to manipulate a part, view a scene, process the information and arrive quickly at a conclusion, e.g. pass or fail. Even when the scene is chaotic, it is relatively easy to train people to pick out the defects that lead to a good or bad determination. For automated systems, this type of inherent analytical capability does not come naturally.

Machine developers need to itemise the human inspection thought process and then mimic it through programming code and part presentation. To do that, there must be a sufficiently detailed and nuanced description of acceptable and unacceptable product. This in itself is a challenge. The creation of an unacceptable product is the exception rather than the norm, so the availability of samples that represent every possible defect or variant of a defect is very low.

ATS has been working on a solution for these difficult applications – a solution that leverages the skill and experience of the trained operator with current vision technology and machine learning.

The ATS M+ solution is a combination of technology and phased implementation. It begins with automated image gathering and manual image classification and then uses this information to eventually teach a system to think like a human inspector. Over time, there is sufficient comparative data collected to validate the performance of the automated inspection solution without ever jeopardising the confidence in the quality of the product released to market.

In order to illustrate how the ATS M+ solution is applied, we will provide an example. For confidentiality purposes, the following example is from a fictional customer, ACME Syringes. ACME is investigating automating their manual inspection process.

ACME SYRINGES

Hypothetical company ACME Syringes produces disposable syringes for hospital, office, laboratory and home use. It has a reputation for a high-quality single-use syringe product family. Key to its quality success are its master-certified inspectors who visually examine every syringe for needle insertion depth, bond inspection, needle tip inspection (shape and orientation) and barrel text (legibility and position), as well as other quality attributes.

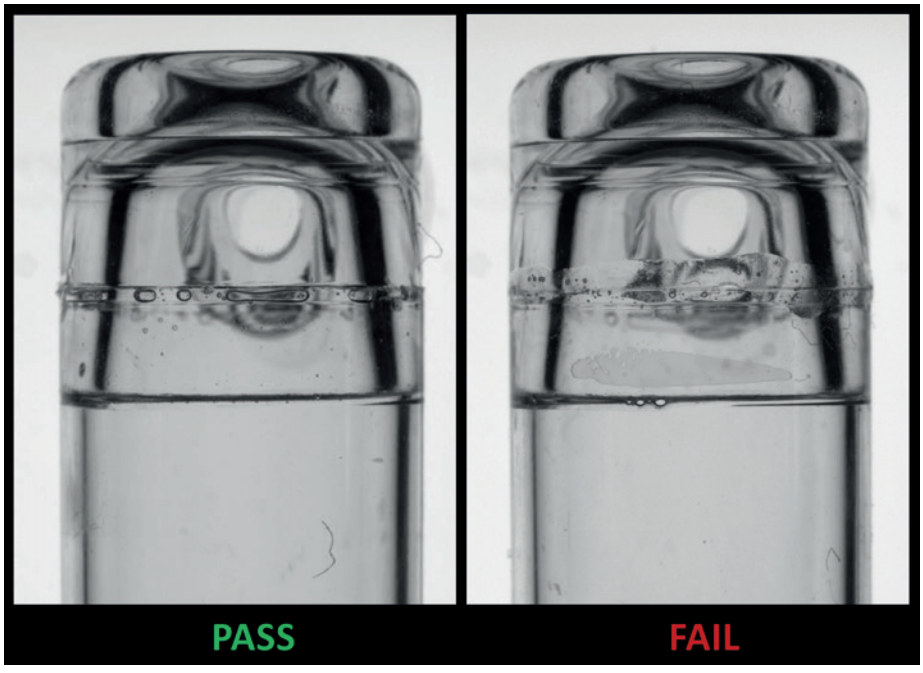

Figure 1: Challenging inspection.

As word of the superior quality and performance gets out, ACME experiences a growing demand for its syringes. This puts a strain on the team of master-certified inspectors, the human resources recruiters, ACME's training department and production's operating budget. ACME's quality group is becoming concerned about the risk of releasing and shipping sub-standard product. Can the reliance on the master-certified inspectors be reduced? Can the inspection process be automated?

A few years ago, and in anticipation of just such a situation, ACME's general manager investigated the feasibility of automating the inspection processes. He talked with several automation providers and imaging experts, only to find that no one would commit to attaining the quality requirements the master-certified inspectors were delivering. They cited as their reason the difficulty of mimicking the decision-making capabilities of the inspectors with the imaging tools available at the time.

Now in a challenging situation, ACME asks the automation experts to revisit the feasibility of automating the inspection processes. The response? Machine learning capabilities in the field of machine vision solutions have taken a major leap forward and now offer some possibilities for automating the inspection process. However, they need 5k–10k images of all different defect types, along with the master-certified inspectors' grading for each. Once in receipt of the images, the automation experts could go away and "teach" an automated solution to do the same inspections and make the same decisions.

This is impossible for ACME to accommodate for two reasons:

1) The current quality level is quite high so it will take months to produce the requested number of images of a defective product.
2) There is no image capture technology on the production lines so there is no image library. The master-certified inspectors look at each syringe directly to make the pass/fail decision and they do not record the defect type when it does occur.

With no image library available, many of the solution providers decline the opportunity. Those that could provide the image capture capability still need ACME to classify the images before they re-engage. It seems that ACME is no closer to an automated inspection solution.

> "The key to reaching the final goal is the employment of the latest advancements in the field of machine learning."

ATS M+ SOLUTION AND IMPLEMENTATION

ACME contacts ATS and ATS immediately identifies its M+ solution as the perfect fit for ACME's needs. No images or samples are necessary as they will be acquired during the phased implementation of the ATS M+ solution. ACME and ATS set to work (Figure 2).

1) Automated image capture

To begin the project and build understanding, ATS works with ACME to determine what it is that the master-certified inspectors look for when manually examining the syringes. In addition, ATS asks about inspection aids like lighting and whether these help to highlight certain syringe features or defect types that matter most when determining quality. Once the inspection needs are clearly defined, ATS integrates the M+ automated camera system with controlled lighting and syringe presentation and orientation capability to ensure the images gathered contain the information needed to show the syringe quality.

2) Manual image classification

ACME is now collecting real images and presenting them in real time to the master-certified inspectors via display screen stations located remotely. The remote location provides a couple of advantages – increased availability of premium floor space and decreased distraction from the production area. The inspectors continue to review each syringe image to determine the pass/fail status. The inspectors' disposition decisions are entered through the station and automatically attached to the images, recorded and passed back to the production line so that the actual syringes are appropriately dispositioned – either a reject bin or packaging and labelling.

In addition, and in anticipation of the next phase, the inspectors classify the images of defective product by the various defect types. The human interpretation of each image is still required in order to build up a library of images that comprise a specific defect type or types.

3) Machine learning from classified images

At this point in the implementation, we have a truly hybrid inspection system in full operation. Automatic image capture combines with human assessment for defect detection and classification. However, we have yet to meet the ultimate goal of replacing the human inspector with a fully automated system.

The key to reaching the final goal is the employment of the latest advancements in the field of machine learning. We will not go into detail here about artificial intelligence and the algorithms of the machine learning discipline. However, it is important to

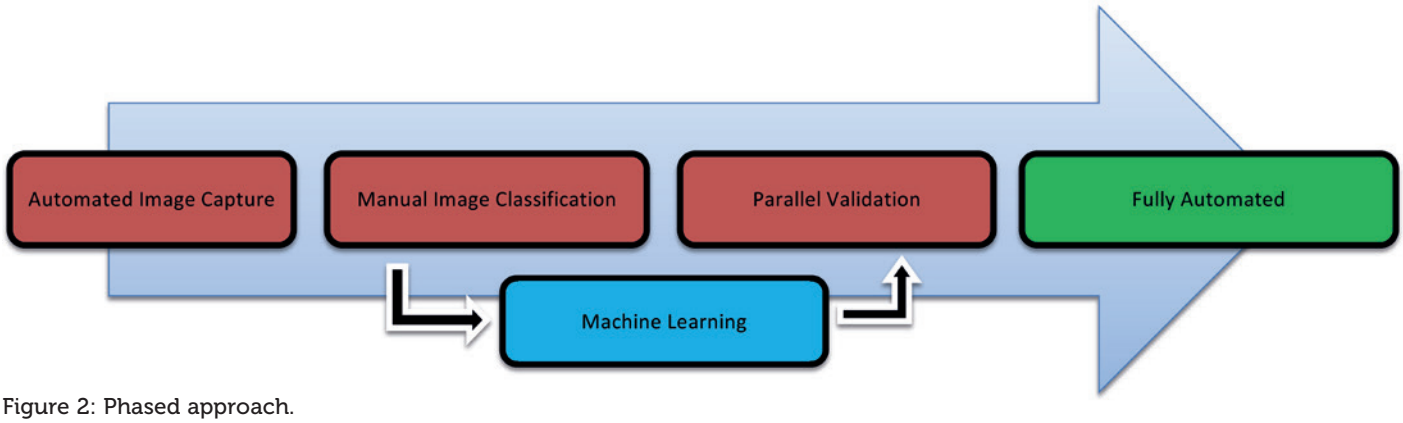

Figure 2: Phased approach.

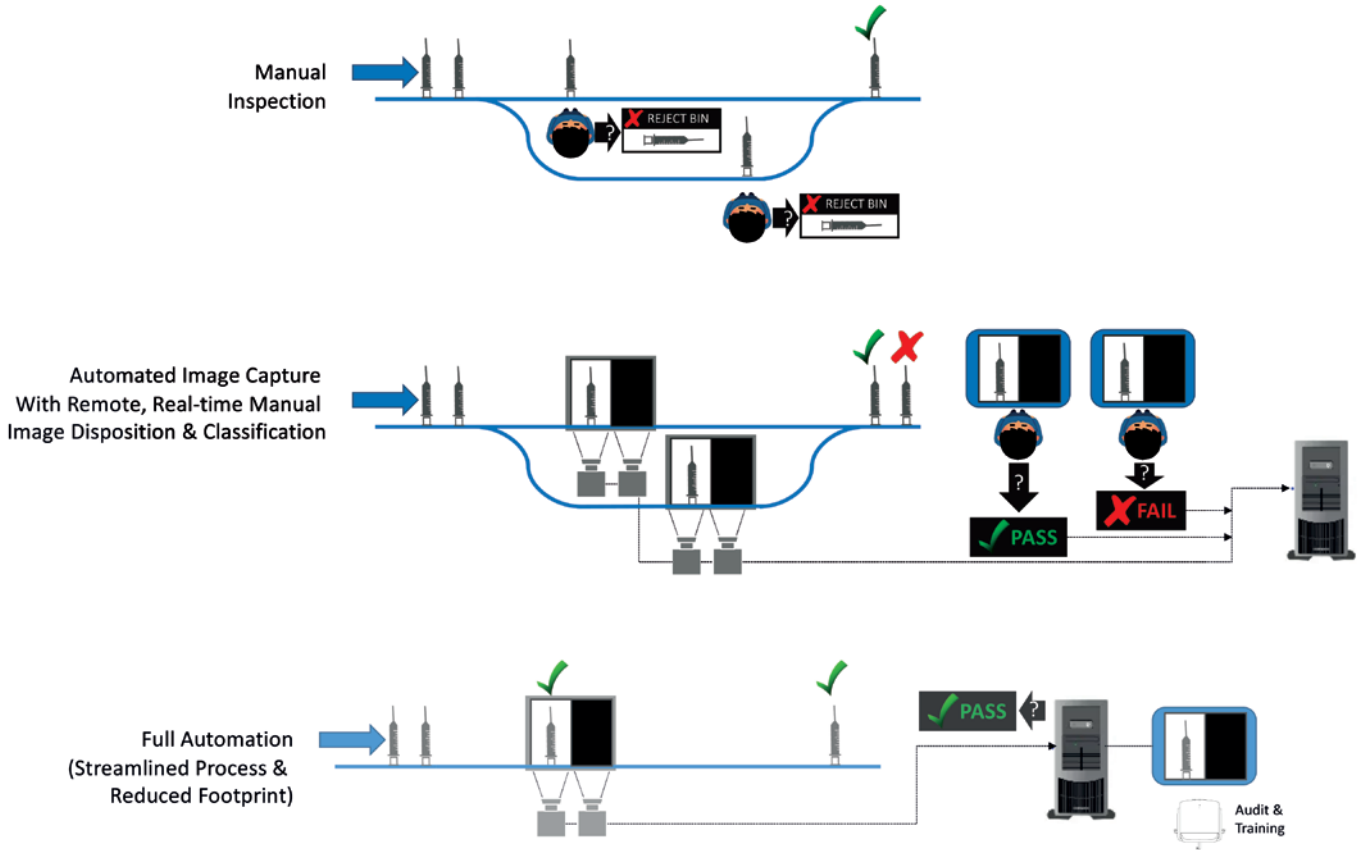

Figure 3: Phased approach and parallel validation in syringe manufacturing.

understand the essence – to "teach" a machine to make the same decisions a human does through the processing of sufficient amounts of pre-classified data such that the machine can make the same classification decisions with the same accuracy as the human on any new unclassified data that it is presented with. In other words, if we can develop the right model using enough quality data, we can develop an algorithm to do what the human does now.

For ACME, ATS' M+ technology is building an image library classified by the master-certified inspectors. ATS is concurrently developing a reliable machine learning algorithm – the other part of the ATS M+ solution. With the image library, it is not necessary to wait for 5k–10k reject images to be processed. ATS creates the model in the background using the data as it becomes available and recycling the library images. With unique approaches and proper algorithm development, it is possible to produce a reliable model with less data.

4) Parallel validation

The challenge now for both ACME and ATS is to prove that the automated inspection system with the machine learning algorithm is as robust and reliable as the current manual inspection. If ACME sells a defective syringe, the end customer is likely to complain and, worst case, a regulatory agency may order a product recall – a very expensive proposition.

The concept of parallel validation involves concurrently running the existing system and the desired future-state system and comparing the results – in this example, the existing manual inspection by the master-certified inspector and the proposed ATS M+ solution. At this point in the phased approach, the inspectors are still classifying all the images collected on the line and dispositioning the syringes accordingly – ACME has not relieved them of that duty, and will not be doing so until the verification that the algorithm is just as good as human judgement is complete (Figure 3).

Once the capability of the machine learning model is established through test cases and verification processes, it is set into operation in parallel with the inspection team. Now, both the inspectors and the ATS M+ solution process every syringe image. The inspectors' and the algorithm's determinations are compared, although the inspectors make the final disposition decision. Further, ACME chooses to pass the same images of defective parts past different inspectors to determine if all inspectors will make the same disposition decision and whether refinement of the definition or alterations to the machine learning model are required. ACME retains full decision-making capability based on these results as to when and if the transition is made to fully automatic inspection. ACME can test the model on the images captured since the beginning of the project. It can continue to test the model with concurrent validation until it is satisfied with the performance. This data-based approach to validating the equivalency and capability of the automated solution provides ACME with the confidence to support a switch to machine inspection.

5) Full automation

After only three months, ACME has gained confidence in the ATS M+ solution's capabilities and reliability and gathered sufficient validation evidence to complete the switch to fully automated inspection. Many of the master-certified inspectors are relieved of the duties of manual syringe inspection and reassigned to other quality-related roles. Some inspection processes were transitioned more quickly than others as the validation evidence was gathered sooner. The machine learning model development and concurrent validation required less data and yet achieved higher accuracy than was originally estimated by some of the other solution providers. Without the ATS M+ solution and the phased implementation, this would not have been attempted, let alone accomplished.

Phase	Description of Enhancements	Benefit
Automated Image Capture	Automatic acquisition and archiving of all images	Robust image archive – remove inspection subjectivity, helps in inspector training
	Images archived with associated product data	Robust image archive - increases quality review opportunities and reduces recall exposure
Image Classification	Rapid disposition of obvious defects	Reduce inspection time; reduce inspector burden; increased throughput
	System provides recommended disposition with rationale to inspector	
Parallel Validation	Queue of images for inspection changes to dynamically balance workload	Reduce bottlenecks; increased throughput
	Inspection performance (timing and accuracy) is tracked and inspectors who require training are identified	Increase inspection accuracy and throughput; increased confidence in fully automated solution
Machine Learning	Self-learning and self-improving algorithms for continual refinement	Increase robustness of inspection, increased likelihood of success for highly complex inspections
Fully Automated	Complete deployment of automated inspection	Increase inspection consistency, accuracy and throughput; reduced reliance on labour
		Reduce production area footprint

Table 2: ATS M+ solution and phased implementation benefits.

CONCLUSION

In summary, the ATS M+ solution facilitates the timely transformation from 100% manual-based visual inspections to 100% automation-based visual inspections. The automated capturing of inspection images, combined with the classification of these same images by trained operators, sets the stage for developing machine learning algorithms. Operating the models in parallel with the manual inspection process builds confidence and data-based evidence of the equivalency and reliability of the automated process. The disciplined execution of a phased implementation plan provides opportunities to assess results and adjust course as necessary. Thus, the risk associated with transitioning difficult inspection tasks to automated inspection is mitigated and benefits can be realised (Table 2).

Machine learning is a powerful new tool in the field of machine vision processing. Inspections that were previously thought to be extremely difficult to automate and validate may now be automation candidates with the proper knowledge, tools and implementation plan. The ATS M+ solution is such a tool. A phased implementation, including concurrent validation, improves the likelihood of success for automating what was previously an impossible inspection.

ABOUT THE COMPANY

ATS is an automation solutions provider to the life sciences, chemicals, consumer products, electronics, food, beverage, transportation, energy, and oil and gas industries. Its offering includes custom automation, repeat automation, automation products and value-added services, including pre-automation and after-sales services, to address the sophisticated manufacturing automation systems and service needs of multinational customers.

ATS provides life science customers with low-risk turnkey, complex, manufacturing systems for medical devices, pharmaceuticals and diagnostic companies. ATS understands that quality of product, assurance of supply and sustainable manufacturing is of particular interest to drug delivery companies. Clients trust ATS with the development of systems for autoinjectors, transdermal devices, syringes, inhalers, electronic meters and devices, IV catheters, tube sets, specialised infusion kits, high-accuracy dispense and placement, filling and packing.

ATS employs approximately 4,400 people at 23 manufacturing facilities and more than 50 offices in North America, Europe, Southeast Asia and China. ATS Automation Tooling Systems, Inc, is publicly owned, and its shares are traded on the Toronto Stock Exchange (TSX: ATA).

ABOUT THE AUTHORS

Steve Wardell is the Imaging Director of the vision engineering team for ATS. For the last eight years, he has been leading the ATS imaging group and its core team of vision engineers. Mr Wardell and this team support all of the ATS automation facilities worldwide and provide hundreds of custom machine vision solutions each year to the life sciences, automotive, energy and consumer goods manufacturing industries. He has a bachelor's degree in mathematics and computer science and started his career 30 years ago at ATS programming controllers and equipment used in high-precision assembly systems. Whether programming, integrating or managing the integration of high-accuracy positioning stages, vision systems or related controls and instrumentation, Mr Wardell has been part of an automation company that has expanded from a one-man shop to a worldwide industry leader today.

Catherine Thacker, PEng, is the Director of Pre-Automation Solutions for ATS Automation. She has provided pre-automation services for ATS since 2006. Prior to ATS, Ms Thacker held various positions with several major life sciences manufacturers, building her expertise in project management, construction, organisational design, production planning and management, facility and maintenance operations, technical transfer, product launches and validation.

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A FIVE-STEP APPROACH TO INNOVATION IN DRUG DELIVERY SYSTEMS

As a full service provider of drug delivery systems, Gerresheimer operates as a one-stop shop for its clients. It has experience across a variety of delivery routes – including inhalers, pen injectors, autoinjectors and prefilled syringes – and works with clients to develop and manufacture both primary and secondary packaging for diverse drug products. Here, Michael Wiglenda, Global Senior Director of the Technical Competence Center & Moldmaking in Germany, explains Gerresheimer's industrialisation offering and the five-step Gate-Model that guides its innovation process.

Gerresheimer has a long track record of helping clients navigate the hurdles that stand in the way of transforming a drug delivery system concept into a mass-produced product ready for market. Less well known is the fact that, behind the scenes, one of the secrets of its success is the way it navigates using its own Gate-Model to guide its innovation process.

The Gate-Model is a five-step process covering the crucial stages of product development – from the concept phase through design and development and pre-production development to mass production development and, eventually, mass production. The aim is to develop new and better products that have a higher chance of succeeding in the competitive marketplace.

> "The aim is to develop new and better products that have a higher chance of succeeding in the competitive marketplace."

The first stage of the Gate-Model – the concept phase – involves developing ideas and product concepts for a client's new device. Using an understanding of market

Figure 1: The small batch production facility has a room with a vacuum for filling toxic materials and, depending on the requirement, it may be done in a protective atmosphere.

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Figure 2: Gerresheimer's small batch production facility has a class 8 clean room in accordance with DIN EN ISO 14644-1.

requirements, the industrial design is drafted, with Gerresheimer taking care of patent management too. Operational concepts are developed as part of the usability engineering, with critical sub-functions considered and models created. In addition, Gerresheimer analyses design concepts as part of usability studies – and performs concept evaluations as well as feasibility studies. The result of the concept phase is a preferred concept, along with a thorough risk analysis and considered market requirements.

Next comes the design and development phase when product requirements are defined, the design is broken down and a client's product is developed in accordance with the relevant regulations. The process required to manufacture the product is developed – and analysed for potential patenting – and simulations and tests are conducted. Functional samples are also created at this stage.

The Gerresheimer service package also includes preselection of suppliers, selection of materials and design of the packaging. The result of this second stage of the Gate-Model is a completely developed product with defined production processes and a design freeze.

The third phase of the process covers pre-production development, which includes design verification and preparation for product verification. Moulds are developed for small batch production, along with specialised machines, and measuring equipment is developed in Gerresheimer's quality laboratory. If necessary, development samples, clinical samples or stability batches are manufactured in a small batch production facility (Figure 1) complete with a clean room (Figure 2) – which can also accommodate low-volume commercial production. The result of this phase is a verified product.

Phase four of the Gate-Model is mass production development – involving industrialisation, validation of production means and preparations for introduction of the product. Mould-making and automation engineering experts design, develop and build the high-cavity injection moulds used for mass production (Figure 3), along with any complex robots and systems required. Gerresheimer also qualifies the production equipment, validates the processes and qualifies suppliers – and prepares the product master file. The result of this stage is mass production means and a product validated for mass production.

The fifth and final phase of the process is mass production, when the product is introduced and lifecycle management begins. The result of this phase is ongoing production of the standard parts and/or standard products.

FULL SERVICE PROVIDER

The Gate-Model illustrates how Gerresheimer is a full service provider of drug delivery systems, operating as a one-stop shop for its clients. It has experience across a variety of delivery routes – including inhalers, pen-injectors, autoinjectors and prefilled syringes – administering active substances via pulmonary inhalation, through the skin or via mucous membranes. It works with clients to develop and manufacture both primary and secondary packaging for diverse drug products – ensuring they are convenient, patient-friendly and delivered to where they are needed quickly and efficiently.

Clients starting a project with Gerresheimer will find a plethora of flexible options available, whether they are looking to develop an existing project or begin from an initial idea. However, Gerresheimer is also a partner for industrialisation of completed drug delivery device projects – working with finalised designs and taking them through to mass production. Projects and products looking to be

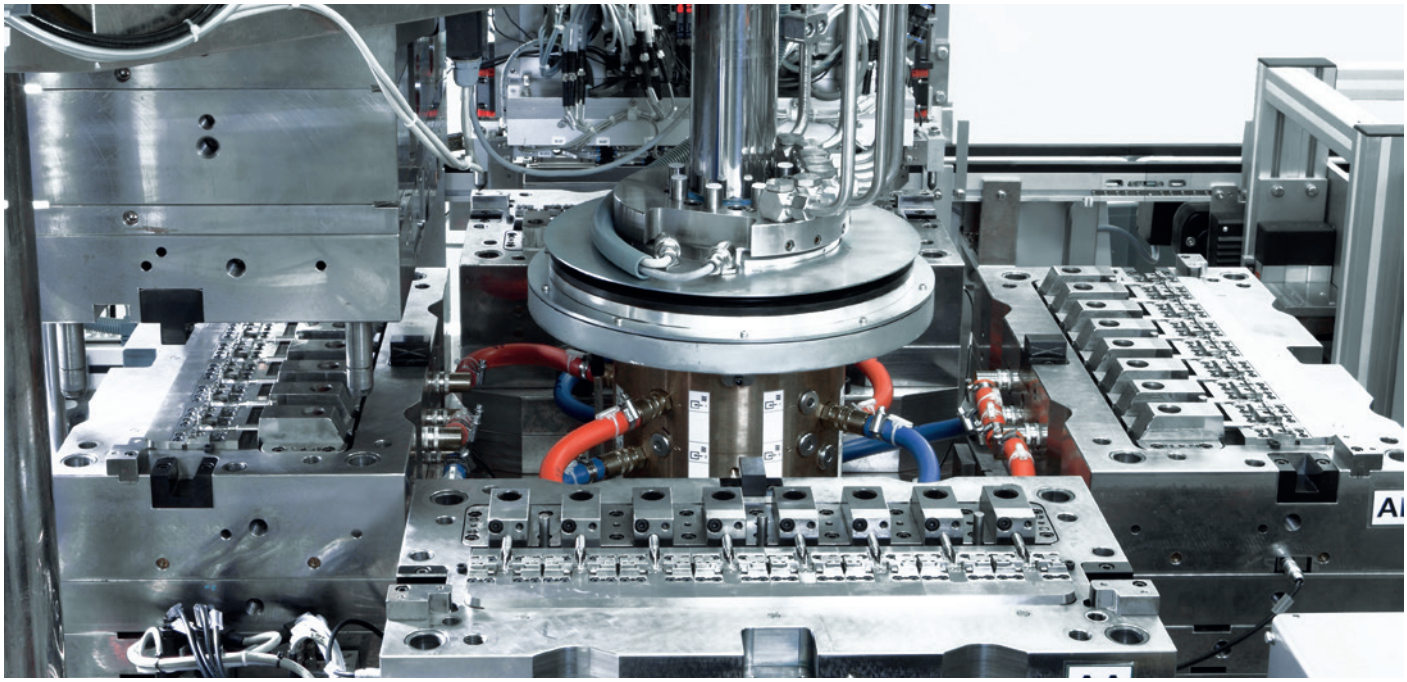

Figure 3: Rotary table with four bottom tool halves for insert moulding of a cannula with ABS for an infusion set.

> "The integrated approach from Gerresheimer has a number of advantages for clients, including reduced development time and risks – meaning products get to market faster."

optimised for polymer process are managed by Gerresheimer's Technical Competence Centers (TCCs) in Wackersdorf and Bünde (Germany), Peachtree City (GA, US) and Dongguan City (China).

TECHNICAL COMPETENCE CENTERS

The TCCs are the "technical heart" of Gerresheimer Medical Systems, in terms of both products and processes. Using the simultaneous engineering method, a TCC maps the entire development process of a product all the way from where it picks up the project through to full-scale industrial production. In the TCCs, designers, engineers and technicians work hand in hand, resulting in drug delivery systems characterised by high quality, functional reliability and capacity to be mass produced in a way specifically designed for plastics.

For example, TCC engineers ensure that all the individual parts of an inhaler can be easily assembled into a solid product to ensure optimum functionality. This care and attention extends to pre-production, applying the highest standards to material selection and assembly technique, as well as drug delivery system functionality. The TCCs' capabilities include:

- Small batch production with an ISO 14644-1 Class 8 cleanroom
- Pilot plant
- Qualification and validation for moulds and special-purpose machines
- Quality laboratory, including its own measuring room with product-specific test equipment
- Functional testing lab
- Mould making and optimisation
- Special-purpose machinery manufacture.

As well as providing design and engineering expertise for polymer components, the TCCs are able to handle production during development, after which full-scale production takes place at Gerresheimer's international production facilities in North and South America, Asia and Europe.

This integrated approach from Gerresheimer has a number of advantages for clients, including reduced development time and risks – meaning products get to market faster.

MOULD MAKING

The mould-making department at Gerresheimer Medical Systems has been manufacturing sophisticated injection moulds since 1958. Its precision injection moulding tools are designed to meet the requirements of the pharma industry relating to precision and size accuracy, surface quality and high output quantities. They are characterised by 100% repeat accuracy, durability and optimised temperature control for short cycle times.

For drug delivery systems, Gerresheimer uses moulds with needle valve nozzles to avoid the formation of strands – i.e. there is no particle formation during separation and removal of the sprue from the mould. It also builds moulds out of rust-proof steel for use in a clean-room environment and ensures there is good ventilation for the moulded parts in the cavities, preventing burn-up and the collection of deposits. Production is fat-free due to the smooth coating of all moveable parts, as well as clean and material-appropriate part removal, achieved via inclined removal surfaces that avoid abrasion.

The mould-making department represents an efficient method of operation, ensuring fast and smooth production of moulds by a segmented structure in mould

> "Uncompromising quality assurance has the highest priority across the entire production process."

production and modification, examining potential changes with test moulds. Furthermore, the department works with replaceable mould inserts for short maintenance and repair times without the need for additional adaptations. Data consistency from the design to all machines and workbenches, as well as the direct link to quality assurance (QA), ensures that moulds are of the highest quality.

Quality Assurance

Uncompromising QA has the highest priority across the entire production process. Precision moulds are ultimately the prerequisite for excellent product quality. As such, only the latest measuring equipment and techniques – for example, computer numerical control (CNC) image processing – are used in the internal measurement lab.

Modern Mould Technologies

More than 65 specially trained employees produce:

- Low- and high-cavity injection moulds, up to 128 cavities, with precision in the micrometre range
- Single- and multi-component moulds
- Indexing plate moulds
- Hot-runner injection moulds
- Moulds for insert moulding – needle and lancet encapsulation
- Stack moulds.

Award-Winning Mould-Making Department

The quality of Gerresheimer's mould-making department was recognised by its top placement in the renowned Excellence in Production competition, organised by the Laboratory for Machine Tools (RWTH Aachen University, Germany) and the Fraunhofer Institute for Production Technology (Aachen, Germany). The TCC of Gerresheimer Regensburg GmbH was named Mould Maker of the Year 2014.

PILOT PLANT

The TCC pilot plant is the practice-oriented competence centre for all injection moulding processes. Here, Gerresheimer proves moulds to check performance and measures, optimises and qualifies moulds. Moulds are sampled using special machinery under near-series conditions and subjected to comprehensive application and processing tests to get them ready for large-scale production.

The sampling and mould optimisation process in the pilot plant forms the basis of the entire component verification. An important stage during this process is the set-up of stable parameter settings for injection moulding, based on a fractional factorial design of experiments (DoE). Additionally, it is at this point that the optical and dimensional component measurements take place in the certified measuring lab, which are then documented in a comprehensive sample test report. Machine and process-capability documentation and mould trials over set time lengths (e.g. four or 24 hours) complete the pilot plant phase.

ANALYSIS AND TESTING

Quality Laboratory

When it comes to drug delivery systems, safety is of the utmost priority. The pilot plant therefore carries out extensive testing in the areas of materials, geometry and function. Gerresheimer has a measuring lab for the geometric measurement of components, assembly units and finished products, a lab for material analyses and a lab for functional testing with product-specific testing equipment.

Optical & Tactile Measurement Technology and Industrial Computer Tomography

By using a measurement lab with the most modern measuring equipment, Gerresheimer ensures that complex mould inserts and filigreed injection moulding parts or assembly units can be measured to extreme levels of precision. The complete set of component measurements is documented in an initial sample test report. The measurement equipment includes:

- Various multi-sensor co-ordinate measuring machines for optical and tactile component measurements
- Universal co-ordinate reading microscopes
- An industrial computer tomograph for the destruction-free measuring and testing of individual drug delivery components or entire assemblies.

Material-Specific, Physical and Chemical Analyses

The material analysis lab is responsible for the inspection and approval of incoming goods and raw materials worldwide. The standard spectroscopic and thermal analyses are:

- Fourier-transform infrared spectroscopy (FTIR)
- Melt mass-flow rate (MFR)/melt volume-flow rate (MVR)
- Differential scanning calorimetry (DSC)
- Thermogravimetric analysis (TGA).

In addition to these, Gerresheimer's extensively equipped lab also offers the possibility of a physical-chemical analysis of viscosity, residual moisture and density, as well as an infrared spectrometer and a thin section microscope. In-house expertise enabling development and execution of customer-specific methods rounds off Gerresheimer's analysis portfolio.

Product-Specific Functional Testing

In the functional testing lab, Gerresheimer develops and qualifies test methods to guarantee compliance with product-specific requirements. It ensures enhanced safety for patients via comprehensive testing of physical product characteristics, product-specific performance tests and statistical data analysis during the product development cycle.

Individual Qualification Packages

The pharmaceutical and medical product industry requires proof of process capability and the reproducible production of an injection mould. QA is therefore given critical importance in both national and international laws and guidelines, signifying a requirement for increased effort and expense with respect to the qualification and validation of moulds in the development and industrialisation phases. As a result of these regulations however, there is less wear on moulds and a higher quality of parts overall, resulting in less waste. But mould qualifications are time and cost intensive. This is why Gerresheimer offers its customers various

"Automation is an integral component of Gerresheimer's product and process development, and leverages its expertise and know-how throughout the concept and design phase."

mould qualification levels depending on the product, its area of application and the regulatory requirement level.

AUTOMATION ENGINEERING

Together with the development and construction of special-purpose machines associated with moulds, Gerresheimer Medical Systems offers its customers high-performance automation solutions. In the pharma and healthcare industries, automation co-ordinated precisely with the product, project and processes has a decisive influence on the quality and economic efficiency of production. The technicians, mechanics, electricians, designers, qualification experts and programmers from the automation engineering department are responsible for this task at the TCCs.

The automation engineering department provides automation competency; develops automation solutions; and specifies, designs, builds, procures and qualifies the following:

- Customer- and part-specific assembly lines
- Testing robots (pressure, flow rate, optical features, force deflection systems)
- Rotary table systems
- Linear systems
- Robots to insert and remove parts
- Packaging systems
- Pre-production equipment
- Pharmaceutical assembly systems
- New generations of glass forming lines (Figure 4).

All the production systems produced by Gerresheimer meet good automated manufacturing practice (GAMP) requirements, as well as US FDA 21 CFR Part 11, and are designed for production in clean rooms in accordance with ISO 14644-1 Class 7/8 or GMP Grade C/D. Being an international manufacturer, Gerresheimer also monitors and assists the start-up of its production equipment on the client's site.

"One focus of expansion is the establishment of small batch production for prefillable glass syringes and cartridges."

The assembly steps and inspection of the modules are done by intelligent camera and inspection systems. As an example, a respiratory patient must be able to easily determine how many doses remain in their inhaler – to avoid the risk of accidentally running out of medication. To facilitate this, Gerresheimer designed an assembly system where the dose-counter function is checked both with a camera inspection system (camera control of the tab position) and a position sensor in the display element after a simulated number of doses, all of which was fully automated.

Automation is an integral component of Gerresheimer's product and process development, and leverages its expertise and know-how throughout the concept and design phase. This means Gerresheimer doesn't wait until mass production to develop automation solutions – it develops them in the prototype and pre-production phase, saving a lot of time.

SMALL BATCH PRODUCTION

Prior to series production, pharmaceutical and medical technology products run through an exhaustive approval process, for which small numbers of units need to be produced repeatedly. For example, small batches may be required as clinical samples, development samples or stability batches.

With its TCCs, Gerresheimer offers clients its own production systems for this task, which are capable of quick and uncomplicated production of development samples, clinical samples or small series at any point in the project.

These facilities include the Class 8 clean room and some of the injection moulding machines have integrated laminar flow covers to create a Class 7 clean-room environment in the injection-moulding area. Project-specific assembly units and specific measuring technologies complete the equipment.

Expansion into Glass

Gerresheimer has expanded its Wackersdorf TCC. The company has invested tens of millions of Euros in creating 3,000 m² of additional space for the development and industrialisation of glass products, such as syringes and cartridges. The task area of the TCC has thus been expanded to include working with glass. Construction began in 2018.

One focus of the expansion is the establishment of small batch production for prefillable glass syringes and cartridges. Once the project is complete, it will be possible to produce pre-series modules from glass forming to ready-to-ship, washed and siliconised ready-to-fill systems. The focus is on syringes and cartridges for sophisticated, biotechnologically manufactured medication, clinical samples for approval or prototypes for process and technology development.

At the same time, glass competence is also being established in the automation systems area (special machine engineering) to develop innovative technologies for glass

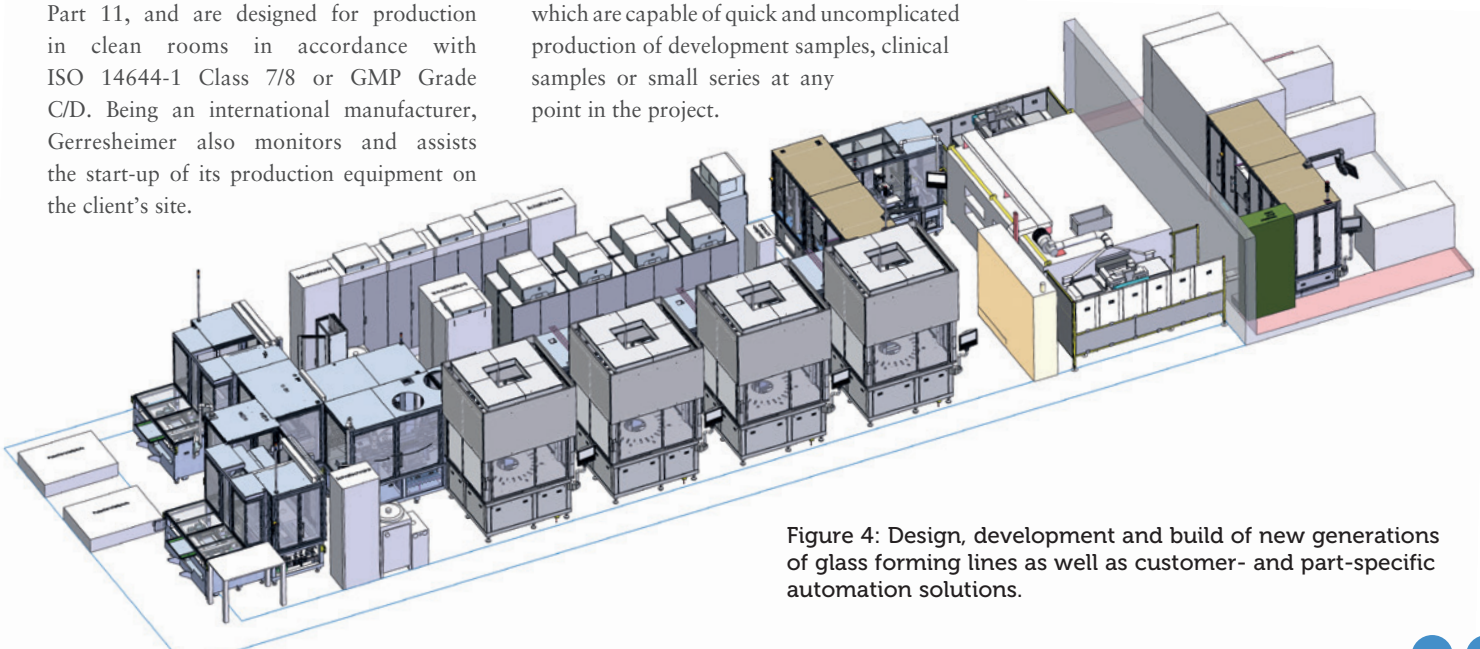

Figure 4: Design, development and build of new generations of glass forming lines as well as customer- and part-specific automation solutions.

forming and automation. In the future, new generations of glass forming lines for syringe production will originate in a co-operation between Gerresheimer's Bünde and Wackersdorf locations, with small batch production and automation systems in Wackersdorf and large batch production in Bünde. This expansion is set to greatly improve Gerresheimer's capacity to develop, optimise and produce innovative glass-based drug delivery systems.

CONCLUSION

Using the equipment and latest technologies in its TCCs, Gerresheimer handles:

- Concept development
- Concept studies
- Ratings and cost analysis
- Industrial design
- Product development
- Process and manufacturing equipment design
- Mould making
- Production (clinical sample, small batch, large batch)
- Automation engineering
- Product Assembly (manual, semi-automated, automated)
- Product finishing
- Pharmaceutical assembly and filling
- Sterilisation
- Packaging
- International distribution.

Gerresheimer is able to join at any phase of drug delivery system development – from initial concept through to final design – and optimise the product for mass production with specialist knowledge and high-quality processes and facilities.

ABOUT THE COMPANY

Gerresheimer is a leading worldwide partner to the pharmaceutical and healthcare industries. Gerresheimer Medical Systems produces customised injection-moulded plastic assembly units, as well as primary packaging made from glass and plastics, worldwide. Gerresheimer works with global players in the pharmaceutical and medical technology industry, producing drug delivery systems across the spectrum. As a full service provider for drug delivery systems, Gerresheimer handles all the phases of the value-creation chain, beginning from the first idea development through to mass production.

ABOUT THE AUTHOR

Michael Wiglenda holds a Dipl-Ing FH in Mechanical Engineering and has more than 20 years of management experience in the plastics processing industry. Mr Wiglenda heads the Technical Competence Centers of Gerresheimer Medical Systems in Germany, China and the US as a Global Senior Director. He was responsible for the creation of the international competence centres as well as for the extension of the German competence centre with pharmaceutical small batch production capabilities. Additionally, Mr Wiglenda is Senior Director of Internal Tool Making.

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Gerresheimer Medical Systems offer assistance with customized drug delivery systems

With Gerresheimer Medical Systems as your partner, you profit from more than fourty years of experience in the development, industrialization and contract manufacturing of customized drug delivery systems. Each year, we produce over 100 million inhalers which meet the full requirements of modern pharmaceutical packaging. As a system supplier, Gerresheimer develops patient-friendly products that are easy to use, provide precise dosing, and efficiently transport the active substance to it's target site. Prior to production, we apply demanding quality standards to material selection, assembly technique and device functionality.

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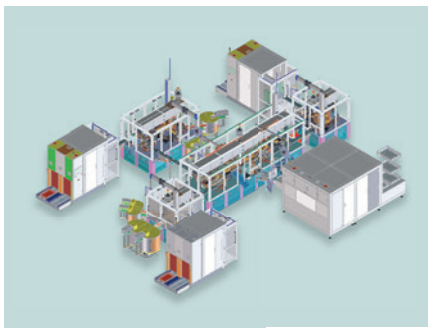

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GATTEFOSSÉ

SYNERGISING EXCIPIENTS TO BOOST SKIN DELIVERY

In this article, Cécile Morin, Technical Communication Executive – Pharmaceuticals, and Delphine Marchaud, Marketing & Innovation Director – Pharmaceuticals, both of Gattefossé, discuss combining polar and apolar excipients in topical formulations in order to produce synergies that maximise the performance of the drug.

The skin constitutes a natural barrier to prevent loss of water from the body and penetration of exogenous substances into it. Understanding its constitution and organisation is essential when formulating efficient topical or transdermal dosage forms.

The "brick and mortar" representation is commonly used to describe the *stratum corneum* (SC), with the corneocytes being the "bricks" and lipids the intercellular "mortar". A gradient of decreasing lipophilicity is observed from the upper layer of the SC down to the dermis.

How vehicles in a formulation interact with the lipid structure significantly contributes to drug diffusion through the different layers of the skin. The major route of drug diffusion through the epidermis is the intercellular path[1] (Figure 1).

Three main steps govern drug diffusion from the formulation to the skin:

- **Solubility:** the formulation must solubilise a sufficient amount of drug to reach an effective concentration at the target site.
- **Partition:** the drug must partition out of the delivery vehicle into the upper layers of the SC.
- **Diffusion:** the drug molecule diffuses through the SC mainly via the intercellular path.

Fick's law applies for passive diffusion, meaning it is driven by drug concentration

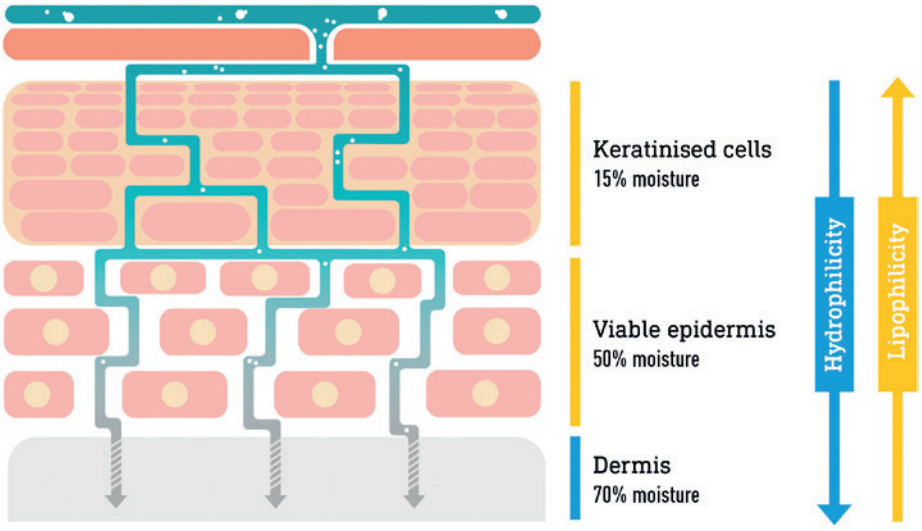

Figure 1: Schematic representation of the structure of the skin.

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and that maximum thermodynamic force is obtained at saturation solubility.

Therefore, the art of formulation consists of choosing the appropriate vehicles and determining their correct ratio to maximise drug solubility in the formulation and subsequent partition in the skin.

Gattefossé has a wide range of lipid excipients for skin delivery, some of which are described in Table 1. This article will focus on Transcutol® P, Capryol™ and Lauroglycol™ and the benefits that arise from their synergistic combination in topical formulations.

LIPID EXCIPIENTS: NATURALLY ADAPTED TO THE SKIN

Lipid excipients, with their high solubilising power and amphiphilic properties, enable modulation of the penetration of the active pharmaceutical ingredient (API) into the SC, and drive API flux.

Transcutol® P is a safe and effective hydrophilic solvent widely used in skin delivery.[2] Transcutol® increases the solubility of both lipophilic and hydrophilic APIs. Furthermore, it can penetrate the SC and interact with the water in the intercellular space.[3]

Capryol™ and Lauroglycol™ are lipophilic solubilisers. They consist of fatty acid esters and can interact with the lipids in the intercellular space. The greatest permeation is observed with excipients containing caprylate (C10) and laurate (C12) fatty acid esters, whereas myristate (C14) and stearate (C18) favour skin-vehicle partitioning.[4]

Polar solvents (e.g. Transcutol®) increase drug solubility in the SC, whereas non-polar solvents (e.g. Capryol™, Lauroglycol™) increase the diffusion parameter of the drug in the SC. Their combination in a formulation has been reported to deliver higher efficiency.

Tradename	Chemical Name	Practical Hydrophile-Lipophile Balance (HLB)
Capryol™ PGMC	Propylene glycol monocaprylate (type I, monoesters >55%) NF	6
Capryol™ 90	Propylene glycol monocaprylate (type II, monoesters >90%) NF	5
Lauroglycol™ FCC	Propylene glycol monolaurate (type I, monoesters >45%) EP/NF	5
Lauroglycol™ 90	Propylene glycol monolaurate (type II, monoesters >90%) EP/NF	3
Transcutol® P	Highly purified diethylene glycol monoethyl ether EP/NF	N/A

Table 1: Gattefossé's main excipients for dermal drug delivery (NF – Compliant with National Formulary monograph, EP – Compliant with European Pharmacopoeia).

Solubiliser	Permeation flux (µg/cm²/h)	Solubility (mg/mL)
Capryol™ 90	6.08 ±2.29	51.3 ±5.68
Lauroglycol™ 90	94.3 ±17.3	15.2 ±1.87
Transcutol® P	0.69 ±0.29	211 ±11

Table 2: Flux and solubility of ketorolac tromethamine with different solubilisers.[5]

A PROVEN SYNERGISTIC EFFECT

The combination of solubilisers is a common practice to maximise drug solubility, thermodynamic force and partition in the skin. Combinations of Transcutol® with other permeation enhancers have been reported in the scientific literature and reviewed by Osborne & Musakhanian (2018). Examples of synergistic combinations using Transcutol® and either Capryol™ or Lauroglycol™ are detailed hereafter.

Example One: Neat Solvents – Ketorolac Tromethamine – Rodent Skin

Cho *et al* (2004)[5] studied the transdermal delivery of ketorolac tromethamine. The study measured drug solubility and permeation through excised hairless mouse skin in various excipients, pure or in mixtures.

Permeation flux was highest for Lauroglycol™ and solubility highest for Transcutol® (Table 2). They then combined Transcutol® with either Lauroglycol™ or

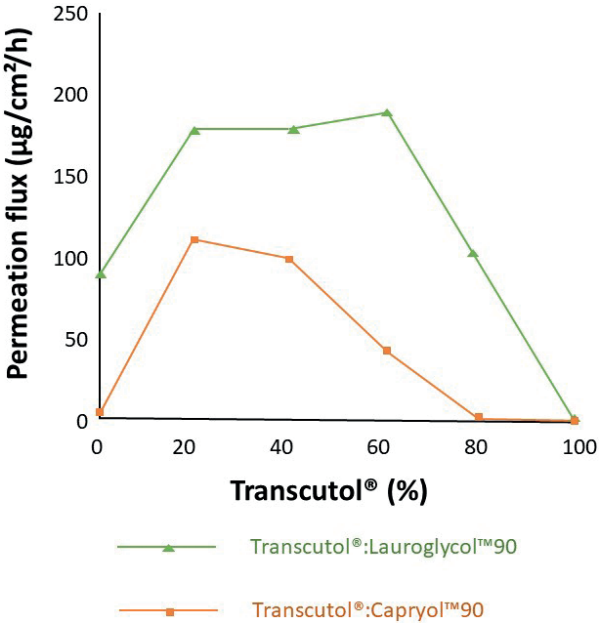

Figure 2: Ketorolac tromethamine flux in neat solvent and solvent mixtures (Adapted from Cho *et al,* 2004).[5]

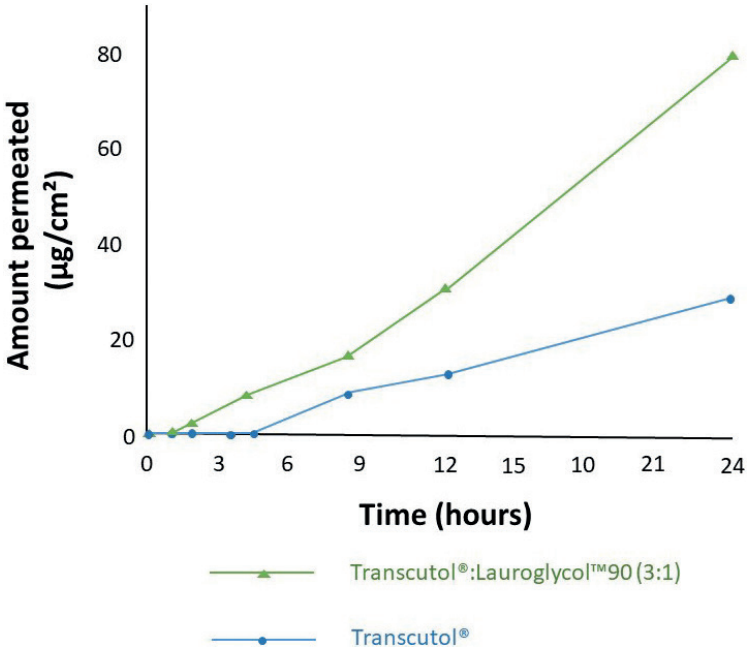

Figure 3: Genistein permeation from a gel containing 25% permeation enhancers (Adapted from Chadha *et al,* 2011).[6]

Capryol™ at different ratios (Figure 2). A 20% increase in permeability was observed for combined Transcutol® and Capryol™ in the ratios 80:20 and 40:60. A two-fold increase in permeation over Lauroglycol™ alone was observed for combined Transcutol®:Lauroglycol™ mixtures in the ratios 20:80, 40:60 and 50:50.

To the authors' knowledge, this study was the first to report a synergistic relationship between the polar solvent Transcutol® and apolar solvents such as Capryol™ and Lauroglycol™.

Example Two: Gel Formulation – Genistein – Human Skin

Chadha *et al* (2011)[6] formulated a gel with genistein and various permeation enhancers and assessed permeation across human skin (Figure 3). A three-fold increase in genistein solubility was observed with Transcutol® alone, whereas the combination Transcutol®:Lauroglycol™ 90 exhibited a 12-fold increase versus the control formulation with ethanol. Similarly, a significant five-fold increase in flux was achieved with Transcutol® alone and a 13-fold increase when combining Transcutol® and Lauroglycol™ 90 (ratio 3:1).

This study confirmed that the synergistic combination of Transcutol® and Lauroglycol™ is efficient when formulated in a gel and tested on human skin.

Example Three: Neat Solvents – Carbenoxolone – Human Skin

Hirata *et al* (2013)[7] tested various solvents, pure or in association, and assessed the skin permeability of carbenoxolone on human skin (Figure 4).

Dimethyl isosorbide (DMI), isopropyl myristate (IPM) and Transcutol® were tested as neat solvent, but permeation at 24 hours was below 0.3 µg/cm². In binary mixtures, synergies were observed, and permeation reached 16.0 and 14.0 µg/cm² at 48 hours for the binary systems Transcutol®:IPM and Transcutol®:Lauroglycol™ FCC, respectively.

Although binary mixtures of solubilisers significantly improved the permeation, the maximum synergy was observed with the ternary composition consisting

> "Some drugs are best served by multi-component solubiliser systems, with three to four excipients, to maximise drug delivery through the skin."

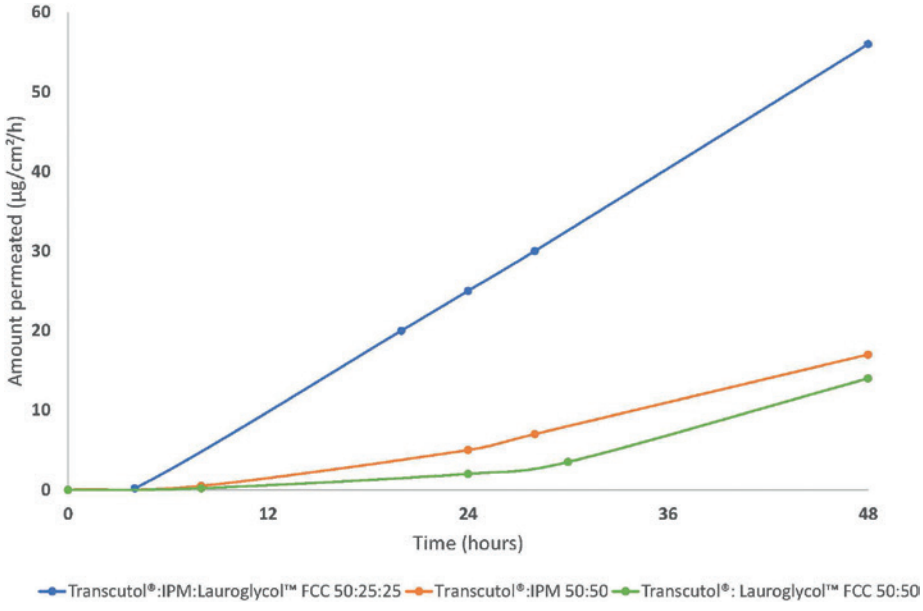

Figure 4: Carbenoxolone permeation from binary and ternary solvent mixtures (Adapted from Hirata *et al,* 2013).

"Each drug is specific and no general rule can be established. Therefore, a case-by-case approach is required to determine which solvents (polar and apolar) are best suited to the drug."

of Transcutol®:IPM:Lauroglycol™ FCC in the ratio 50:25:25, with flux reaching 56 µg/cm²/h.

This study highlights that for some actives, a ternary solubiliser system is needed to reach sufficient level of permeation.

Example 4: Gel Formulation – Diclofenac Sodium – Human Skin

At Gattefossé, diclofenac sodium was used as a model drug and formulated in gels for permeability studies on human skin (Figure 5). Although the permeation obtained with the binary system propylene glycol (PG):Lauroglycol™ FCC was quite high (about 100 µg/cm²), the best performance was achieved with a quaternary system consisting of Transcutol®P, IPM, PG and Lauroglycol™ FCC (Figure 5) and a permeation of about 120 µg/cm².

This study highlights the fact that some drugs are best served by multi-component solubiliser systems, with three to four excipients, to maximise drug delivery through the skin. The formulator has to determine the optimal ratio of polar and apolar solvents for the drug, and this can only be done on a case-by-case basis.

CONCLUSION

Drug delivery to the skin is a challenging process requiring solubilisation, partition and diffusion of the drug through the different dermal layers. Each drug is specific and no general rule can be established. Therefore, a case-by-case approach is required to determine which solvents (polar and apolar) are best suited to the drug. However, when developing a formulation, one has to keep in mind that even when permeation is low with individual excipients, combination can produce synergies, as was demonstrated with Transcutol® P in association with Lauroglycol™ or Capryol™.

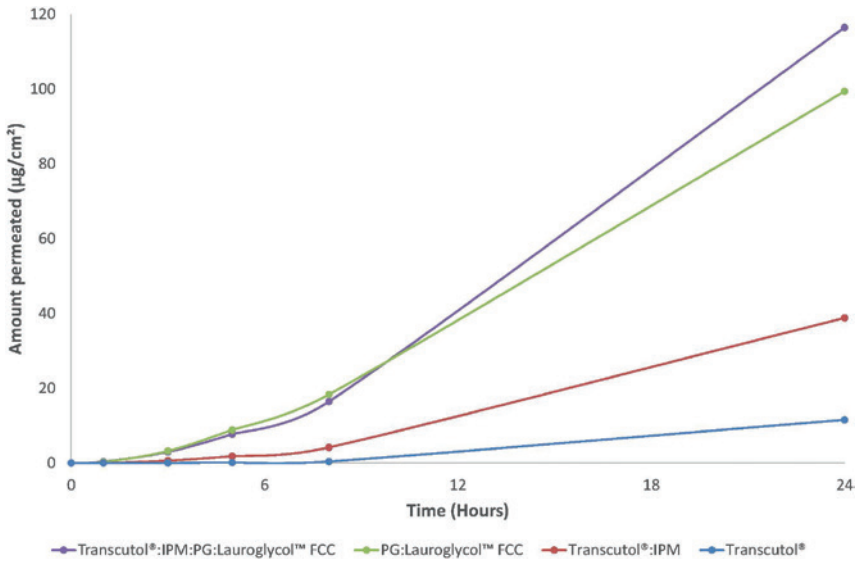

Figure 5: Diclofenac sodium permeation through human skin from various gel formulations (Gattefossé in-house study).

BOX 1: GATTEFOSSÉ'S DRUG DELIVERY OFFERING

ORAL DRUG DELIVERY

Functional lipid excipients that are designed to meet the most pressing formulation challenges in oral drug development:

- **Solubility/Bioavailability Enhancement:** Lipid-based drug delivery systems consisting of single or multiple excipients, forming oily formulations, self-emulsifying (SEDDS) and self-micro-emulsifying (SMEDDS) formulations or micellar solutions, for APIs with poor solubility, permeability or bioavailability.
- **Modified Release:** Lipid matrices that are water-insoluble and do not swell or erode when in contact with aqueous media. They form an inert matrix from which the drug diffuses slowly over time allowing for modified or sustained-release of API.
- **Protection and Taste Masking:** Excipients that form a film coating around the drug particle for taste-masking and protection of sensitive APIs when used in melt processes.
- **Lubrication:** Excipients that act as a lubricant for challenging tablets and capsules, with inert excipients eliminating drug-excipient incompatibility issues.

TOPICAL DRUG DELIVERY

Functional lipid excipients are used to formulate creams, lotions, ointments, foams and oily and aqueous gels:

- **Optimised Sensorial Experience:** Improved texture and sensorial properties positively impact the patient experience and adherence to treatment. Optimising stability, texture and sensorial qualities of a topical product can be achieved with the selection of the right combination of emulsifiers and consistency agents.
- **Solubilisers:** Transdermal drug delivery can be achieved by the selection of suitable solubilisers, skin penetration enhancers and solvents to enable passage through the skin.

RECTAL & VAGINAL DRUG DELIVERY

Functional lipid excipients are used to formulate suppositories, pessaries, creams, ointments and foams:

- Optimisation: Well-established hard fat bases for suppositories and pessaries optimise drug delivery for a wide range of APIs and manufacturing equipment.
- Emulsifiers: Alternative dosage forms for rectal or vaginal mucosal delivery can be formulated with safe, non-irritant emulsifiers and thickeners.

INTERNATIONAL TECHNICAL SUPPORT

With an international network of technical representatives and Technical Centers of Excellence in the US, France, India and China, Gattefossé provides bespoke technical and regulatory support to accelerate drug development.

ABOUT THE COMPANY

Gattefossé is a leading provider of lipid excipients and formulation solutions to healthcare industries worldwide, with an in-depth knowledge of lipid excipient physicochemical and functional properties. The company has an international network of technical representatives and Technical Centers of Excellence in the US, France, India and China. Gattefossé provides bespoke technical and regulatory support to accelerate drug development.

ABOUT THE AUTHORS

Cécile Morin is a food engineer with a long experience in communication concerning food, pharmaceutical and cosmetic ingredients. She is in charge of print and digital communication for Gattefossé Pharmaceuticals.

Delphine Marchaud graduated in 1996 from the School of Applied Sciences, University of Montpellier (France) in Physicochemistry and completed her training with a Master 2 in Pharmaceutical Technologies. In 1998, she joined Gattefossé, managing the Pharmaceutical Application Laboratory. From 2006 she took the lead of the Pharmaceutical Technical Division, with a team of scientists developing lipid based drug delivery platforms and novel applications. Since January 2014, Ms Marchaud is Director of the Marketing & Innovation department for pharmaceuticals at Gattefossé.

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Z.BLIZZARD AUTOMATION SYSTEM – IT DOESN'T GET MORE TAILOR-MADE THAN THIS

Here, Berthold Schopferer, Product Manager, System Technology, ZAHORANSKY Automation & Molds, explains how the company's integrated syringe manufacturing and assembly equipment allows maximum customisation and full customer involvement.

Customisation, an aspect valued so highly by consumers when it comes to coffee or specially made muesli, and standard practice in the auto industry, has now also become firmly established in the world of mechanical engineering with the mould and machine engineering specialist ZAHORANSKY Automation & Molds. We can build our systems in series in different versions, greatly adapted to each specific customer. We implement the modularity that is both desired and required on a one-to-one basis – naturally based on the principle that our customers' products will meet the high quality requirements that are not just promised but demanded in the medical technology sector. This is because we want and need to ensure that our systems pose no risk whatsoever to the product or a person's health.

THE CUSTOMER'S ROLE IN THE DEVELOPMENT

The following examples of configuration options for the Z.BLIZZARD (shown in Figure 1), an automation system which includes injection moulding, show what is meant by the high degree of customisation of the systems. In current systems, if so desired, more than ten camera systems can ensure continuous monitoring of the product during the manufacturing process, as well as an integrated 100% X-ray system for quality assurance after assembly (Figure 2).

It is virtually impossible to achieve more comprehensive quality assurance based on today's technology. Nevertheless, maximum machine capability is important as the foundation for achieving high process capability. Our customers also have the advantage that they can

Figure 1: The Z.BLIZZARD produces ready-to-fill staked-needle syringes from COC/COP polymers with a very high autonomy time.

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Figure 2: More than ten camera systems can ensure continuous monitoring, as well as an integrated 100% X-ray system for quality assurance after assembly.

source these options from a single supplier. After all, when it comes to X-ray technology, certain standards and guidelines must be followed, and not everyone has that capability. We have our own specialists in this area, therewith providing the customer with legal and regulatory security.

The same careful approach also applies to cleanroom modules. Here, ZAHORANSKY uses industry-proven systems to enable our customers' products to be produced in hygienic conditions. The customer is also involved in many more decisions: How should the bevel be oriented? Should it be straight or bended? Which area should the camera cover? Is integrated X-ray inspection needed? Should the Z.BLIZZARD be equipped with additional access doors? These and other details are worked out in close collaboration with the customer, then implemented in exactly the same way. Customers are involved from an early stage, guiding the entire design and manufacturing process, which usually takes 12 months.

GOOD MANUFACTURING PRACTICE GUARANTEED

Some of our customers bring with them their own knowhow regarding special components or technologies that they need in order to manufacture their final product. Of course, this doesn't always have to be the case; we are also happy to provide customers with comprehensive advice and recommendations. However, if our customers already have fixed ideas about tried-and-tested modules or technologies,

> "Just because something works in the laboratory does not necessarily mean it will work in an industrial environment."

and they want these to be integrated into our systems, we do prove these very carefully in advance. After all, just because something works in the laboratory does not necessarily mean it will work in an industrial environment. Therefore, in some cases we also develop these solutions ready for series production.

It is so important that the customer is closely involved in the development process whenever possible and as much as they wish to be. Whether and how much development work must be carried out with the customer is examined at an early stage of the project and, naturally, follows GMP guidelines.

The customer is provided with evidence to prove that the implementation of the proposed solution will be audit-proof. We must be able to show why something does or doesn't work. When it comes to machine manufacturers, that is what separates the best from the rest. For us, 100% means 100%. We also think in a future-oriented manner for our customers. That is to say, even after we have delivered and installed a customer's Z.BLIZZARD system, it is still important to us that they have an innovative and future-proof piece of equipment.

SAME LOOK, DIFFERENT CHALLENGES

The interior of the Z.BLIZZARD is but one opportunity for customisation. If the Z.MISTRAL, which handles downstream processing, and the Z.LODOS palletising system are also connected (Figure 3) the entire process chain, from granulates to packaged COC/COP polymer ready-to-fill staked-needle-syringes (PFS), can be covered with a very long autonomy time.

It's worth mentioning that although most PFS look quite similar and have an identical basic function, each customer brings different challenges and different specifications. Obviously, we have to take these into account when manufacturing the equipment.

ZAHORANSKY customers opt to make their PFS out of plastic (Figure 4). The major advantage here compared with their glass-syringe counterparts is that

the needle is overmoulded and not fused or glued in. The conditions during the glass syringe's fusing process, which involves temperatures of more than 1000 °C and materials with high temperature-resistance such as tungsten, cause heavy metals to be released. These heavy metals may migrate into or interact with the glass container and can later also be detected in the product, even though the containers are subsequently washed, dried and sterilised. Moreover, the plastic variety also benefits from a minimised risk of breakage and greater design freedom.

TOP QUALITY

The Z.NFS Needle Feeding System (Figures 5 & 6) also guarantees that needles are processed on a "first-in, first-out" basis. The system can be filled with the required quantity of cannulas, which are then used in order for the batch. This prevents the needles from remaining in the system for longer periods. The Z.NFS can separate between four and 32 needles or cannulas at up to 12 cycles per minute; in other words, up to 400 units per minute. It can currently handle needle diameters from 0.2 mm and lengths up to 45 mm. The Z.NFS is also an integrated system and thus guarantees maximum purity in the production process, since there is no human contact and the process is cleanroom compatible. One can hardly imagine higher quality in medical device manufacture or a greater degree of customisation for the producer.

Figure 3: The connected Z.MISTRAL and Z.LODOS can cover the entire process chain, from granulates to packaged PFS.

ABOUT THE COMPANY

ZAHORANSKY AG is a full-range supplier in machinery and production lines, sophisticated, innovative injection moulds and automation equipment. The company operates with over 700 associates at production sites in Germany, Spain, China, India and the US. System Technology offers across-system solutions for the injection-related automation. These systems are based on injection moulds by ZAHORANSKY Automation & Molds GmbH and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules. ZAHORANSKY Automation & Molds GmbH serves the areas Industrial Automation and Medical Devices, with pre-configured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making ready-to-fill prefillable syringes as primary medical packaging.

Figure 4: The Z.BLIZZARD manufactures plastic PFSs that boast several advantages over their glass counterparts.

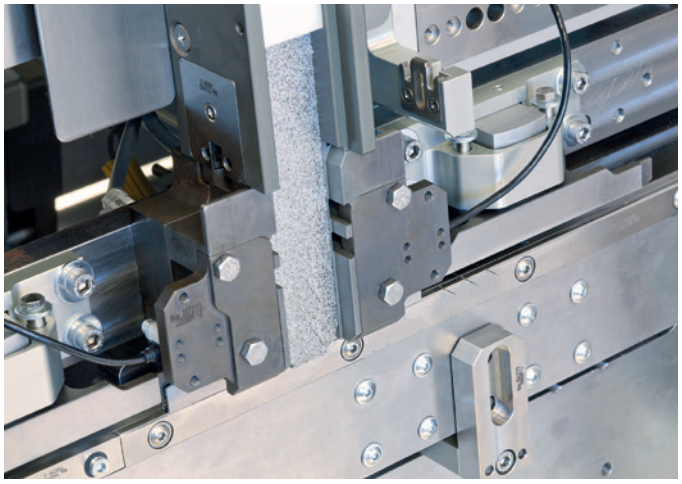

Figure 5: The Z.NFS needle feeding system, which can separate 4-32 needles or cannulas at up to 12 cycles per minute.

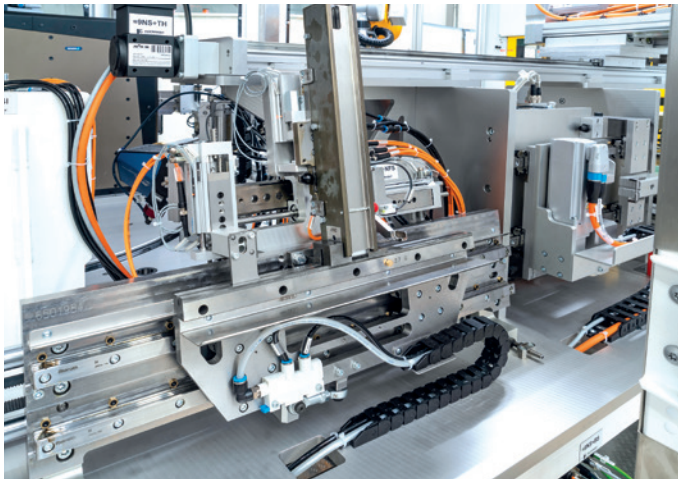

Figure 6: The Z.NFS combined with the Z.BLIZZARD forms an integrated system for a cleanroom compatible process with no human contact.

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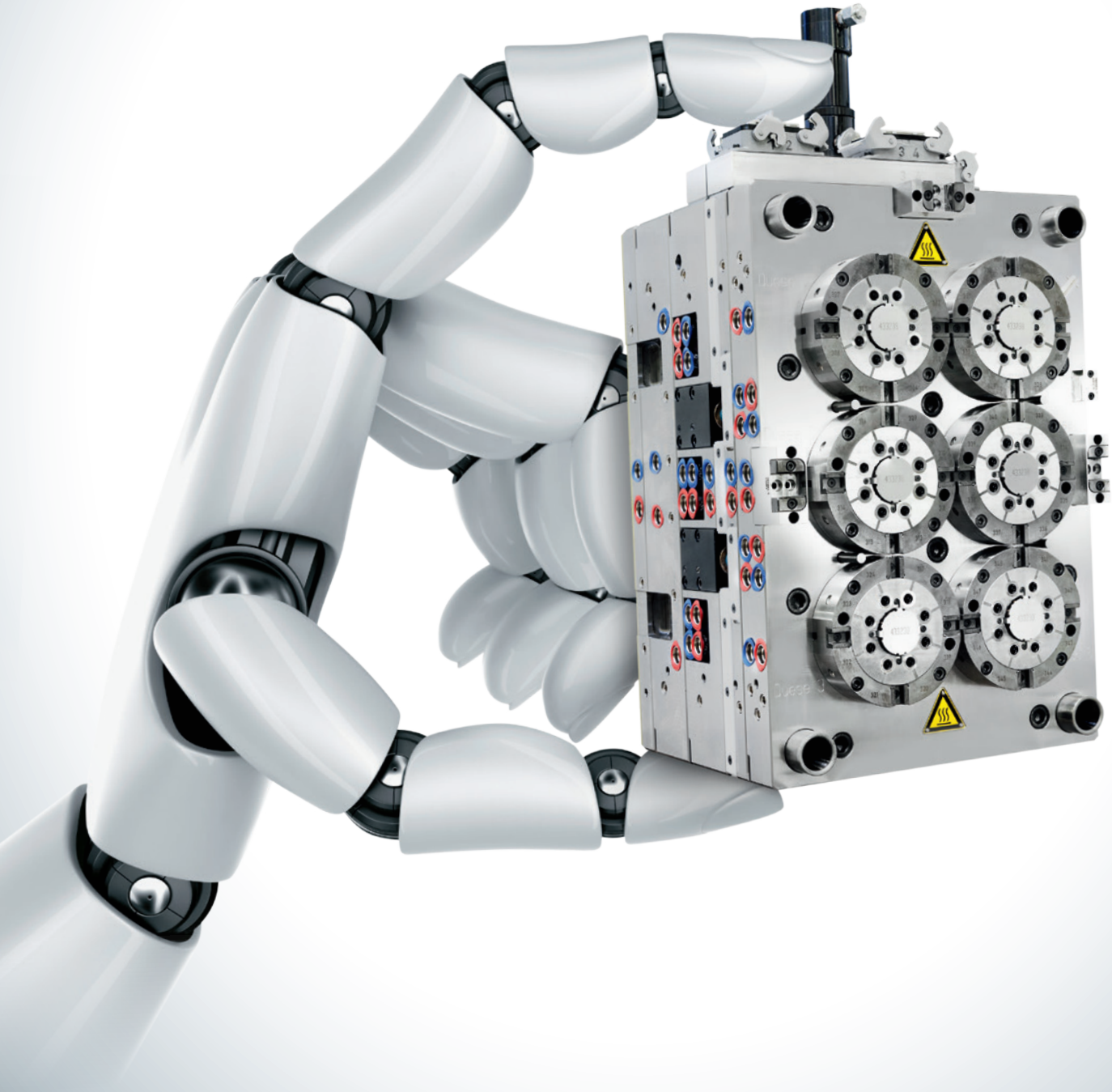

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CECILE HALTE, BD

Cécile Halté currently works as Senior Program Manager, Acute Care Segment, for BD Medical – Pharmaceutical Systems. Dr Halté's focus areas are planning the product development roadmap over lifecycle of products for acute care and ensuring successful cross-functional execution of projects. She joined BD in 2012 and held various positions in project management, with increasing scope of responsibility. Dr Halté graduated from Ecole des Mines de Paris (France) and holds a PhD in nanobiotechnology from Université Joseph Fourrier (Grenoble, France).

In this interview, Dr Halté discusses validation studies of the BD Sterifill Advance™ plastic prefilled syringe, which is intended for use in the hospital setting by healthcare professionals either for manual bolus injections, or with infusion pumps.

Q Could you tell us why BD Sterifill Advance™ syringe has been developed, and describe it briefly?

A In a randomised and controlled study, and other studies, it was shown that healthcare workers needed significantly more time for administering drugs to patients when preparing *de novo* in comparison with prefilled syringes in a stressful situation.[1-4]

To address this issue, BD developed BD Sterifill Advance™, a common delivery system used in high stress, acute care settings, which is a plastic prefillable 50 mL syringe to be compatible with syringe infusion pumps. Later, BD Sterifill Advance™ was extended to smaller sizes in order to provide users with additional dose flexibility in use with pumps (20 mL sizes) or for manual bolus injections (5, 10, 20, 50 mL sizes).

BD Sterifill Advance™ 5, 10, 20 and 50 mL syringes are intended to be used by healthcare workers in hospitals, with infusion pump use (for 20 and 50 mL syringes) and manual use (for 5, 10, 20, 50 mL).

Q What are the method and design elements of these validation studies?

A BD ran two studies to evaluate the expected impact of the new BD Sterifill Advance™ 50 mL prefillable syringe on infusion performance, healthcare workers' daily practice and the consequences on patient and healthcare worker safety, comparing infusion with a syringe pump using either the BD Sterifill Advance™ 50 mL or a conventional system (drug in ampoule, diluent, disposable syringe).

> "In a randomised and controlled study, it was shown that healthcare workers needed significantly more time for administering drugs to patients when preparing de novo in comparison with prefilled syringes in a stressful situation."

A total of 300 infusions were performed by a biomedical technician with BD Sterifill Advance™ 50 mL (150) or a conventional syringe (150). Drug delivery performance was evaluated at four different flow rates (1, 5, 25 and 100 mL/h), using five commonly used syringe pumps.

To assess the usability of BD Sterifill Advance™ 50 mL 120 healthcare workers simulated 960 infusions, 480 with Sterifill Advance™ and 480 with a conventional syringe (Figure 1).

In the second study, 60 healthcare workers were enrolled and each of them performed eight infusions with BD Sterifill Advance™ 50 mL and two infusions with a conventional syringe in order to assess the usability of BD Sterifill Advance™ 50 mL with syringe pump.

BD conducted a third human factors validation study to assess the usability of BD Sterifill Advance™ for the manual infusion (5 and 20 mL formats) and in use with pumps (20 mL format).

For the human factors validation study for the manual injection, each of 15 enrolled healthcare workers performed

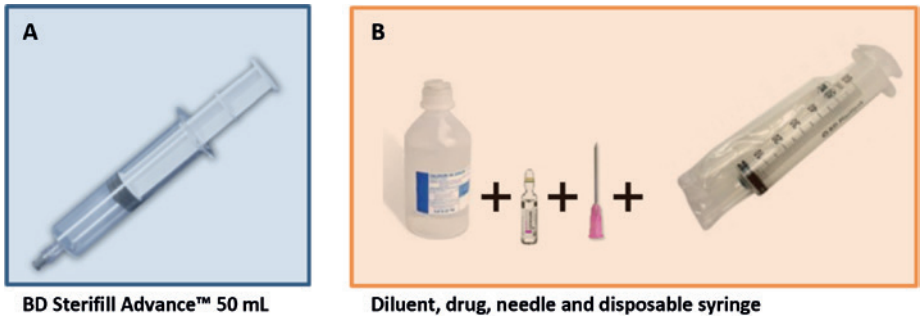

Figure 1: Materials required for infusions using BD Sterifill Advance™ 50 mL syringe (A) and disposable syringe (B).

13 injections with BD Sterifill Advance™ syringes and two simulated injections with a conventional syringe.

Usability was evaluated through instructions for use (IFU) compliance. An observer recorded use errors (detection of operational difficulties). The steps successfully performed were counted, per simulation, per phase and overall, and errors were classified according to their risk class.

Q What were the objectives of the Human Factor Validation studies?

A The objectives of these studies were to demonstrate, using different syringe pumps, that drug delivery performance of BD Sterifill Advance™ 50 mL prefillable syringe is as good as the performance obtained with classic conventional syringe. Other objectives were to demonstrate, using human factors validation, that the Sterifill Advance™ 5, 10, 20 and 50 mL prefillable syringes are safe for patients and healthcare workers both for pump (20 and 50 mL) and manual (5, 10, 20 and 50 mL) use.

Q What were the results concerning BD Sterifill Advance™ prefillable syringe in combination with infusion pump?

A BD Sterifill Advance™ 50 mL syringe was found to be compatible with the tested syringe pumps at different flow rates (1, 5, 25 and 100 mL/h). Interestingly, BD Sterifill Advance™ had a significantly shorter T95% on average than the tested conventional syringe (Figure 2). By comparison with disposable syringes, the new Sterifill Advance™ 50 mL prefillable syringe reaches a satisfactory and equivalent drug delivery performance.

75.83% of the simulations were performed with BD Sterifill Advance™ by healthcare workers without any error (i.e. with eight IFU compliant steps) (Figure 3). At the steps scale, when using BD Sterifill Advance™, IFU compliance is fully satisfactory, with 96.48% of the steps having been correctly performed, and only 3.52% of the steps were performed with handling errors (IFU non-compliant) (Figure 4). Therefore, usability of the BD Sterifill Advance™ 50 mL syringe used in combination with infusion pump is validated.

From the last human factors study results, BD Sterifill Advance™ 20 mL syringe format has also been found safe and effective.

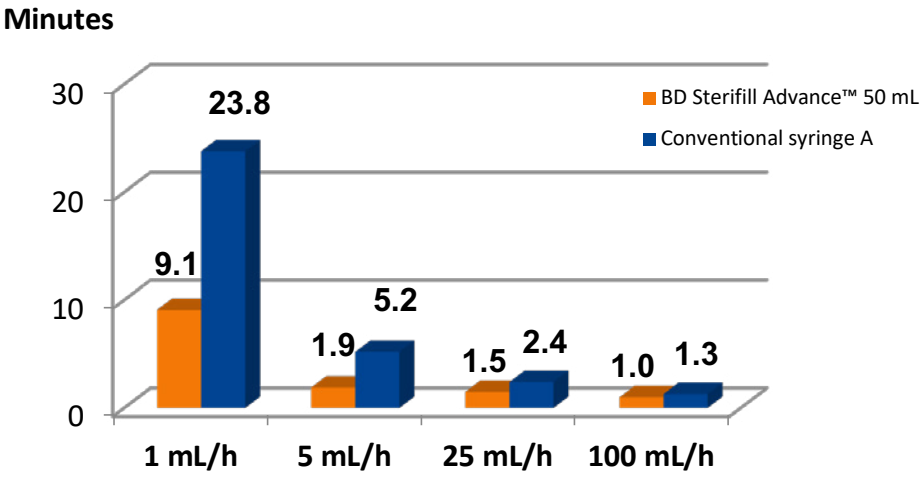

Figure 2: Time to reach 95% of targeted flow rate. Time in minutes to reach 95% of targeted flow rates using BD Sterifill Advance™ 50 mL syringe and another conventional 50 mL syringe with pump. N= 30 simulated infusions for both syringes.

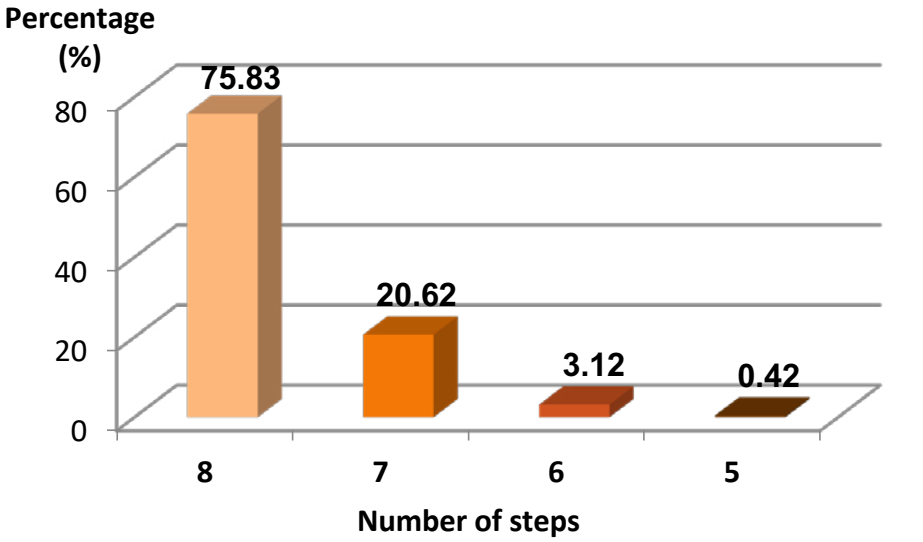

Figure 3: IFU compliance with BD Sterifill Advance™ 50 mL syringe per step. Percentage of BD Sterifill Advance™ 50 mL simulations achieved with 1 to 8 IFU compliant steps. No IFU non-compliant steps between 1 and 4 steps. N = 480 simulated infusions.

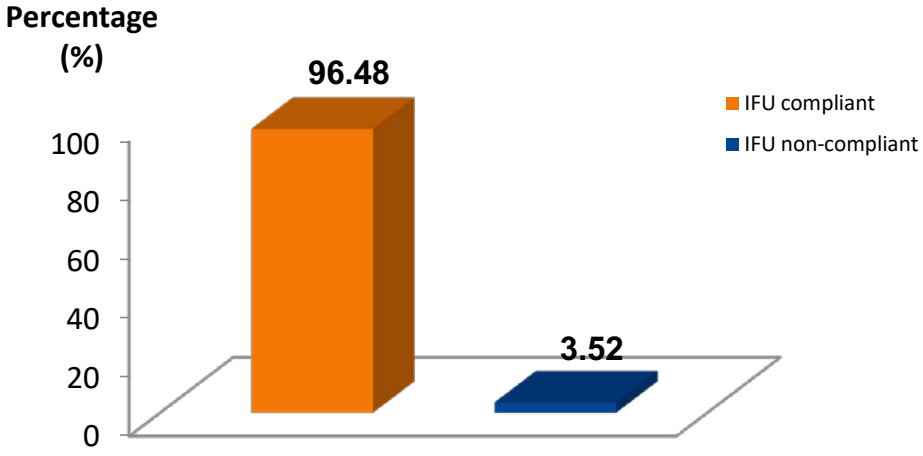

Figure 4: Overall IFU compliance with BD Sterifill Advance™ 50 mL syringe. Percentage of BD Sterifill Advance™ 50 mL simulations steps IFU compliant or non-compliant. N = 3840 steps.

Q **Focusing on manual use, what results were obtained?**

A In manual use, IFU compliance of BD Sterifill Advance™ 5, 10, 20 and 50 mL syringes was satisfactory (99.1% of steps correctly performed, on average) (Figure 5). The IFU were efficient based on results showing more than 99% success of the users that did not read the IFU. Overall, BD Sterifill Advance™ prefillable syringe was found to be intuitive (over 99% IFU compliance for all kinds of simulation at the first injection). Due to this high product intuitiveness, no perceptible learning effect was noted.

Therefore BD Sterifill Advance™ syringes have been found to be safe and effective when used by healthcare workers in hospitals for manual utilisation with no residual risk found for this application. It is important to note that these syringes may improve healthcare worker efficiency and effectively help save time for delivering treatment. Indeed, BD Sterifill Advance™ 5, 10 and 20 mL syringes have been found to be easy to use, useful and usable for experienced healthcare workers, with a faster preparation time compared with conventional syringes.

> "BD Sterifill Advance™ 5, 10 and 20 mL syringes have been found to be easy to use, useful and usable for experienced healthcare workers, with a faster preparation time compared with conventional syringes."

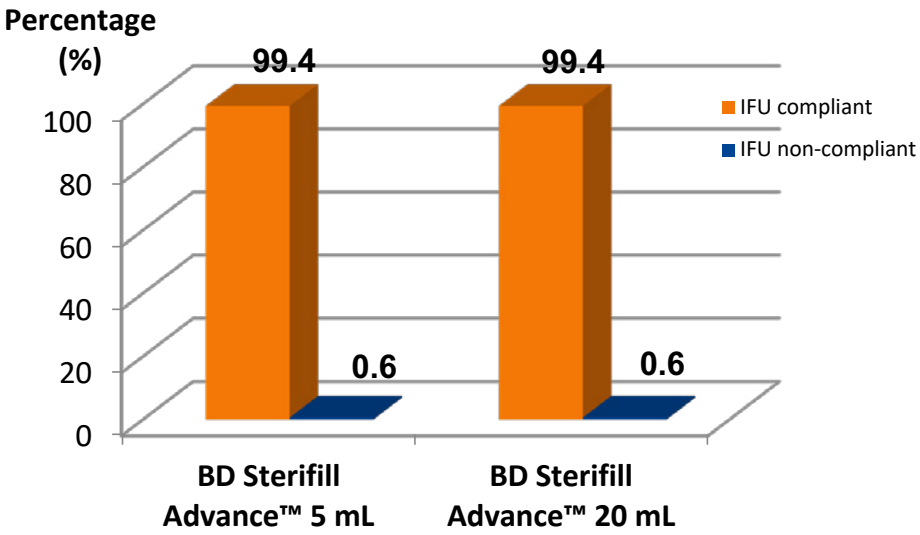

Figure 5: IFU compliance with BD Sterifill Advance™ 5 and 20 mL syringes. Percentage of steps performed IFU compliant and IFU non-compliant using BD Sterifill Advance™ 5 and 20 mL syringes for manual injections. N = 75 simulated injections with respectively BD Sterifill Advance™ 5 and 20 mL syringes.

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