INDUSTRIALISING DRUG DELIVERY

ON drugDELIVERY

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INDUSTRIALISING DRUG DELIVERY

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

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ELECTROSPINNING: A PROMISING APPROACH TO CONTINUOUS MANUFACTURING FOR PHARMACEUTICALS

Here, Blair Brettmann, PhD, Assistant Professor, Georgia Institute of Technology, discusses the present advantages and challenges, as well as the future potential, of electrospinning as a continuous manufacturing technique for the pharmaceutical industry.

INTRODUCTION

Continuous manufacturing of pharmaceutical products has generated significant industrial and academic interest in recent years. Most current pharmaceutical manufacturing processes operate in batches, with each operation occurring in discrete steps and equipment being fully restarted between each batch. Continuous manufacturing, already employed in many industries including chemicals, paper and plastic, and food products, can streamline the process, moving material through all stages without stopping.

Pressure to decrease manufacturing costs and increase capability for in-line process analytics has driven the establishment of research centres at universities, including the MIT-Novartis Center for Continuous Manufacturing of Pharmaceuticals, the Center for Structured Organic Particulate Systems based at Rutgers University, and the University of Strathclyde Centre for Continuous Manufacturing and Advanced Crystallisation. Well-publicised commercial ventures, such as Janssen's Prezista®, have used continuous manufacturing for industrial production, and other, less publicised, ventures are being explored throughout the industry.

> "Continuous manufacturing has significant benefits as compared with batch throughout the production process, including high production efficiency, low physical footprint, capability for in-line real-time process analytics, and translatable know-how from other industries."

Continuous manufacturing has significant benefits as compared with batch throughout the production process, including high production efficiency, low physical footprint, capability for in-line real-time process analytics, and translatable know-how from other industries. The Brettmann Lab at the Georgia Institute of Technology specifically focuses on downstream continuous manufacturing; starting with the synthesised and purified drug and finishing with the final drug product. Continuous manufacturing provides additional benefits for downstream processing and formulation, in particular providing platforms to reduce solids handling and make better use of designer excipients.

DOWNSTREAM CONTINUOUS MANUFACTURING TECHNOLOGIES

Three promising technologies for downstream pharmaceutical manufacturing are very familiar in the polymer processing field:

- Melt extrusion
- Film formation
- Electrospinning.

These typically take a mixture of polymer excipient and active pharmaceutical ingredient (API), with solvent added for film formation and electrospinning, and process them together as a liquid (melt or solution). The liquid is solidified in the process, be it by cooling or drying, to obtain a final solid form (Figure 1). These technologies minimise or eliminate the need for handling solids and improve the degree of mixing between the polymeric excipient and the API, at times resulting in molecular-level mixing. This is in contrast to traditional blending and

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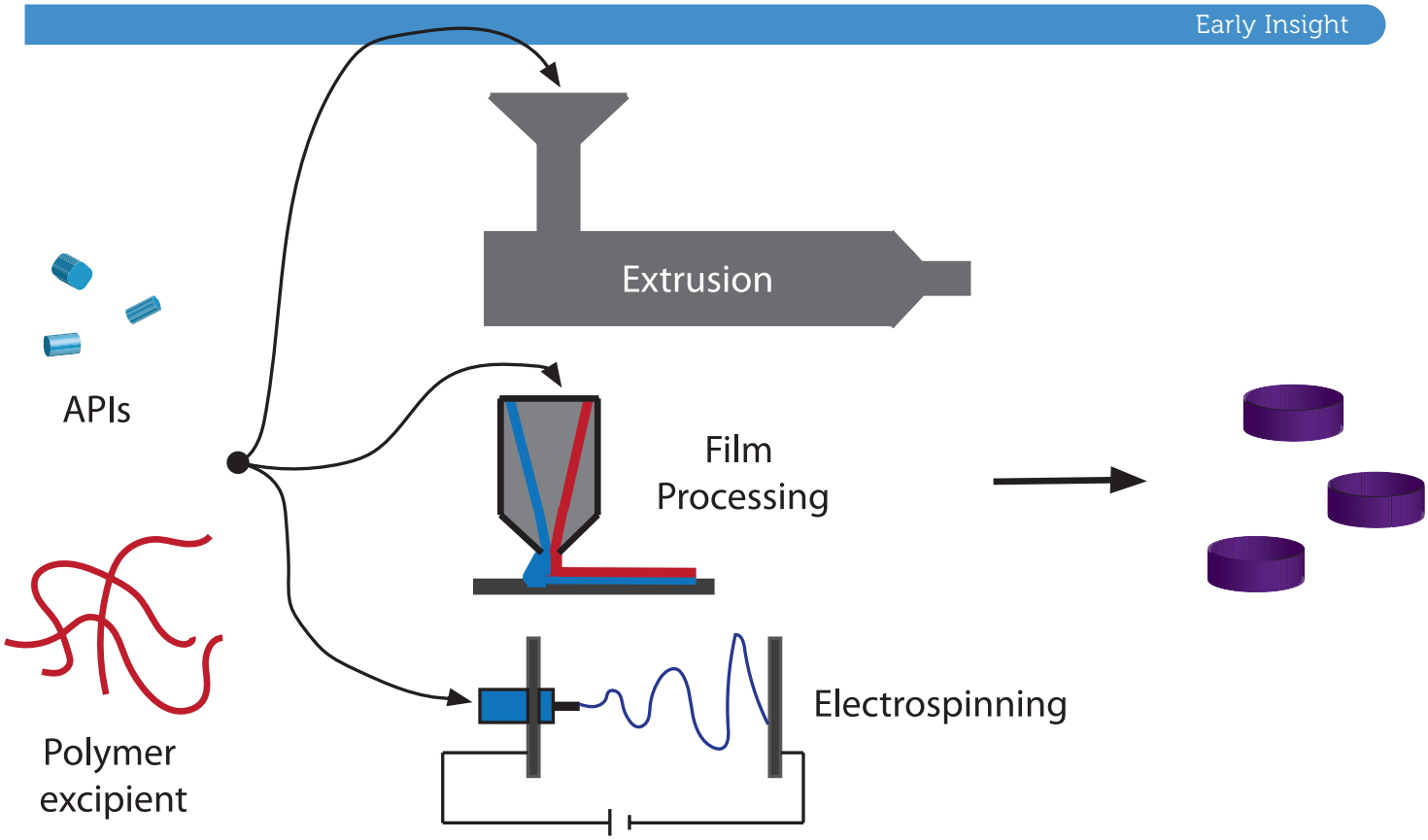

Figure 1: Downstream manufacturing processes for drug products inspired by polymer processing.

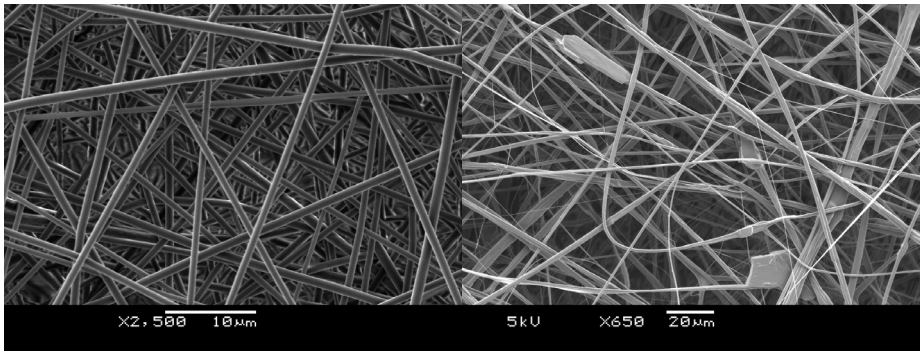

Figure 2: Electrospun fibres containing APIs: A) Amorphous API and B) Crystalline API.

> "Electrospinning is particularly exciting, as it results in fibres of 100-1000 nm in a non-woven mat. The high surface area of the fibres is advantageous for rapid dissolution and the morphology is of interest in drug delivery beyond oral dosage forms."

granulation processes, where micron to millimetre sized powder particles are mixed.

Of these processing methods, electrospinning is particularly exciting, as it results in fibres of 100-1000 nm in a non-woven mat. The high surface area of the fibres is advantageous for rapid dissolution and the morphology is of interest in drug delivery beyond oral dosage forms. The scale of the electrospun fibres is similar to that of the extracellular matrix, potentially making them viable scaffolds for tissue engineering. Furthermore, the surface chemistry of the fibres is readily adaptable, providing unique potential to modify the material to be compatible with any environment.

In addition to the high surface area fibres, electrospinning provides advantages to downstream pharmaceutical manufacturing through its exceptionally high evaporation rate, which freezes the mixture as it is mixed in solution state. It is also readily performed at many scales, from 0.05 g/hr for a single needle to 200 g/hr for a 1 metre electrode using free surface electrospinning, which can be further increased to larger production scales using many electrodes in series. The end product of electrospinning is a non-woven fibre mat (Figure 2), which can be delivered as a film-based dosage form or can be chopped and pressed into tablets.

OVERCOMING THE CURRENT DRAWBACKS OF ELECTROSPINNING

Electrospinning has been developing as a production technology in recent years, with great progress being made in scale-up and process understanding. Commercial products from electrospun fibres are on the market for applications such as air and water filtration, cell culture scaffolds and sound-proofing materials. While large companies such as Samsung, Toray and Boeing have incorporated it into their R&D programmes, pharmaceutical manufacturing is still lagging behind, in part due to drawbacks unique to small-molecule pharmaceutical drug products.

- **Limited materials are "electrospinnable":** Electrospinning requires a significant amount of high-molecular-weight polymer to maintain fibre shape during spinning. In the Brettmann Lab at Georgia Tech, we work to improve electrospinning of high loadings of particles, expanding the functional material types that are amenable to electrospinning applications.

- **Controlling the API form:** Due to the high evaporation rates during electrospinning, the API is typically in the amorphous form following electrospinning, altering its resultant physicochemical properties. A particle electrospinning process is able to to electrospin crystalline API, however traditional solution electrospinning can still be used to prepare amorphous solid products.
- **Importance of API-excipient interactions:** The molecular interactions between the API and excipient will impact the performance of the drug product, and with electrospinning these interactions are enhanced due to the intimate level of mixing. In a well-understood system, this can be an advantage, as the polymers can be used to improve drug performance, but a thorough consideration of molecular behaviour with respect to processing is essential to control the therapeutic effect and mitigate potential side effects.

The Brettmann Research Group at Georgia Tech takes an integrated approach to product development, considering chemical molecular behaviour and microstructural effects in developing new processes for a variety of applications. Fundamental studies are performed to look at how the drug molecule interacts with the polymer excipient, going as far as to design and select polymers to have desired interactions for both processing and dissolution properties. Beyond that, technology solutions are designed to broaden the applicability of electrospinning in downstream pharmaceutical processing, examining the effect of the process on the solid drug form, the stability and the functionality.

ELECTROSPINNING AMORPHOUS SOLID DISPERSIONS

A large number of newly-discovered drugs are poorly water soluble, inhibiting their development as pharmaceutical products. One approach to improve the solubility of these APIs is to formulate them as amorphous solids, where the molecules are arranged in a disordered fashion, rather than in crystalline lattices. The amorphous form is in a higher energy state, thereby exhibiting higher solubility, but it also has a tendency to crystallise over time during storage and delivery. Rational formulation with a polymeric excipient as an amorphous solid dispersion can help stabilise the amorphous form, maintaining the higher solubility for an acceptable period of time to use as a drug product.

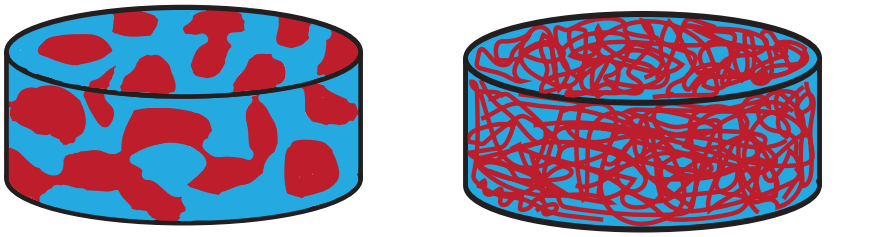

Figure 3: Melt extrusion results in phase separation of the polymer and API, while electrospinning results in homogeneous mixtures down to a 10 nm length scale.

> "To obtain fibres containing crystalline API, a suspension of drug particles must be prepared, where the API is insoluble in the solvent and API crystal particles are dispersed throughout the polymer solution."

One challenge in preparing amorphous solid dispersions is achieving sufficient mixing between the polymer excipient and the API to provide good stability. More physical separation between API molecules and a greater occurrence of molecular interactions, such as hydrogen bonding, between the API and polymer will improve stability, but this is difficult to achieve via powder blending. Some improvements have been made using twin screw extrusion, where the API is melted and mixed with the polymer, but in many cases this has not been sufficient.

Due to the extremely rapid evaporation during electrospinning, the degree of mixing between the API and polymer is higher than with other methods. It has been shown that, following melt extrusion, a 4:1 Aliskirin:polyvinyl pyrrolidone mixture was phase separated with domains of at least 40-80 nm, while the same formulation prepared by electrospinning was homogeneous with no measurable domains larger than about 10 nm, as illustrated in Figure 3.[1] Processing into a solid form via electrospinning demonstrated improved mixing of the drug with the polymer excipient, which has been shown to improve amorphous form stability.

In addition to providing a greater barrier to diffusive ability of drug molecules and rearrangement from the amorphous to crystalline form, the increased surface area provided by electrospun fibres makes them particularly valuable for poorly water soluble drugs. The dissolution rate of the API will also be enhanced with greater exposure to the solvent, and the very high surface-to-volume ratio of electrospun fibres provides a distinct advantage over compressed powders, which are typically prepared from particles that are tens of microns in size.

Adding the advantages conferred by

ABOUT THE AUTHOR

Blair Brettmann received a BS in Chemical Engineering at the University of Texas at Austin and a PhD in Chemical Engineering at MIT, focusing on continuous manufacturing of pharmaceuticals. Following her PhD, Dr Brettmann was a Senior Research Engineer at Saint-Gobain, where she worked on polymer-based coatings and dispersions for commercial applications. Later, Dr Brettmann served as a postdoctoral researcher in the Institute for Molecular Engineering at the University of Chicago. Her lab at Georgia Tech designs and studies new processing and characterisation technologies, focusing on linking molecular- to micron-scale phenomena to product performance, with a specific interest in applications for pharmaceutical product development.

"Adding the advantages conferred by continuous processes in general to the unique advantages of electrospinning makes this a particularly exciting approach for preparation of amorphous solid dispersions."

continuous processes in general to the unique advantages of electrospinning makes this a particularly exciting approach for preparation of amorphous solid dispersions. While the feasibility of using electrospinning to prepare amorphous solid dispersions has been demonstrated, the future of the process as a commercial manufacturing method will rely on two key challenges:

1. **Integration into manufacturing:** Applying scale-up principles from other electrospinning applications and developing the best downstream processing of the fibre mats into deliverable dosage forms.
2. **Formulation of products with desired performance:** Developing a fundamental understanding of API-polymer molecular interactions and determining the performance of the materials, particularly when additional excipient compounds are added, such as surfactants and disintegrants.

ELECTROSPINNING CRYSTALLINE DRUG PRODUCTS

Drug products containing crystalline API make up a majority of oral solid dosage forms on the market today and are likely to remain important in the industry. Though electrospinning has specific advantages for amorphous solid dispersions, the technology can also be applied as a continuous manufacturing process for crystalline drug products, rendering it a highly versatile approach for APIs of interest developed in the drug discovery pipeline.

For the amorphous products, the API is dissolved in a common solvent with the polymer, promoting molecular-level mixing. To obtain fibres containing crystalline API, a suspension of drug particles must be prepared, where the API is insoluble in the solvent and API crystal particles are dispersed throughout the polymer solution. The suspension is then electrospun, an approach referred to as "particle electrospinning".

Using two model crystalline APIs, albendazole and famotidine, it was shown that the particles can be electrospun into fibres at a 1:2 particle:polymer ratio.[2] The fibres encapsulated the crystalline API particles in the centre of the fibre and, since the particle size (approximately 10 µm average diameter) is larger than the fibre size (approximately 2 µm average diameter), they appeared as protrusions along the length of the fibre (Figure 2B). When the fibres were pressed into tablets, they showed significantly higher dissolution rates than compressed powder tablets due to the distribution of the particles throughout the fibres; the encapsulation of the crystals in the polymer prevented aggregation and, since the polymer is hydrophilic, allowed release and rapid dissolution of the crystals.

Recent work has explored particle electrospinning further, particularly examining the effect of large particles on electrospinnability and morphology at loadings ranging from 1:5 to 2:1 particle:polymer. Three factors were found to strongly impact the process:[3]

1. **Particle density:** Particles with a high density will settle out of the electrospinning solutions, resulting in lower loadings than expected in the fibres.
2. **Particle aggregation:** If the particles aggregate prior to electrospinning, the entire aggregate will be electrospun, resulting in a "bunches of grapes" morphology.
3. **Fibre to particle diameter ratio:** When the size of the fibres is much smaller than the particle, the particles may be entrapped within the fibre mat in a net-like structure rather than encapsulated within the fibres.

Particle electrospinning is a promising method for downstream continuous manufacturing, maintaining the benefits of high surface area and solution processing, while allowing for crystalline APIs in the final drug product.

FUTURE OUTLOOK

Continuous manufacturing has the potential to transform pharmaceutical manufacturing, particularly in downstream manufacturing where additional benefits, such as reduced solids handling, can also be readily integrated. Building off of current polymer processing technologies, melt extrusion, film processing and electrospinning are particularly ripe for development into the pharmaceutical space. Amorphous solid dispersions produced via electrospinning provide higher degrees of mixing between an API and polymer excipient, resulting in improved therapeutic products, while crystalline API can be incorporated into the fibres using a particle electrospinning process.

To be ready for integration into pharmaceutical manufacturing lines, further development is needed to adapt scale-up methods from established electrospinning applications and to determine the ideal methods to transform fibre mats into tablets. To take maximum advantage of further benefits of electrospinning, fundamental studies need be conducted to fully understand polymer-API interactions during electrospinning and during dissolution of the final products. New studies for rational design of polymers as advanced excipients[4] can readily be integrated into the formulation for electrospun drug products. These advances will lay the groundwork for electrospinning to be a highly competitive downstream manufacturing process for the pharmaceutical industry.

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GERRESHEIMER

A COMPREHENSIVE APPROACH TO PHARMA INDUSTRIALISATION PARTNERING

As a company offering contract services at every stage of drug delivery system development, Gerresheimer has a wealth of expertise and history in industrial-scale production. Here, Michael Wiglenda, Global Senior Director Technical Competence Center & Moldmaking Germany, explains Gerresheimer's industrialisation offering in detail.

INTRODUCTION

The gulf between a drug delivery system concept and a mass-produced product ready for market is a vast one. Gerresheimer knows this well, as a full service provider for drug delivery systems that operates at every phase, from initial idea development through to full industrial manufacture. Gerresheimer handles:

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

With this full suite of services available, Gerresheimer is a one-stop-shop for getting a pharmaceutical product to market. The company has experience across a spectrum of delivery routes, including inhalers, pen-injectors, autoinjectors and prefilled syringes. In co-operation with its customers, Gerresheimer develops and manufactures both primary and secondary packaging for diverse drug products, ensuring that a product is convenient, patient-friendly and delivered to where it is needed quickly and efficiently.

> "Gerresheimer is a one-stop-shop for getting a pharmaceutical product to market. The company has experience across a spectrum of delivery routes, including inhalers, pen-injectors, autoinjectors and prefilled syringes."

Customers 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, as this article will discuss, 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 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, with regard to both products and processes (Figure 1).

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Figure 1: Inside a TCC.

"The irrefutable quality of Gerresheimer's mould-making department was recognised by its top placement in the renowned "Excellence in Production" competition, which is organised by the Laboratory for Machine Tools and the Fraunhofer Institute for Production Technology."

Using the simultaneous engineering method, a TCC maps the entire development process of a product all the way from where they pick the project up 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 fashion 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 the 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.

MOULD MAKING

The mould-making department at Gerresheimer Medical Systems has a long history and strong tradition. As early as 1958, the department started manufacturing sophisticated injection moulds, primarily for cleanroom production. Gerresheimer's precision injection moulding tools are designed to meet the high requirements of the pharmaceutical 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 (Figure 2).

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

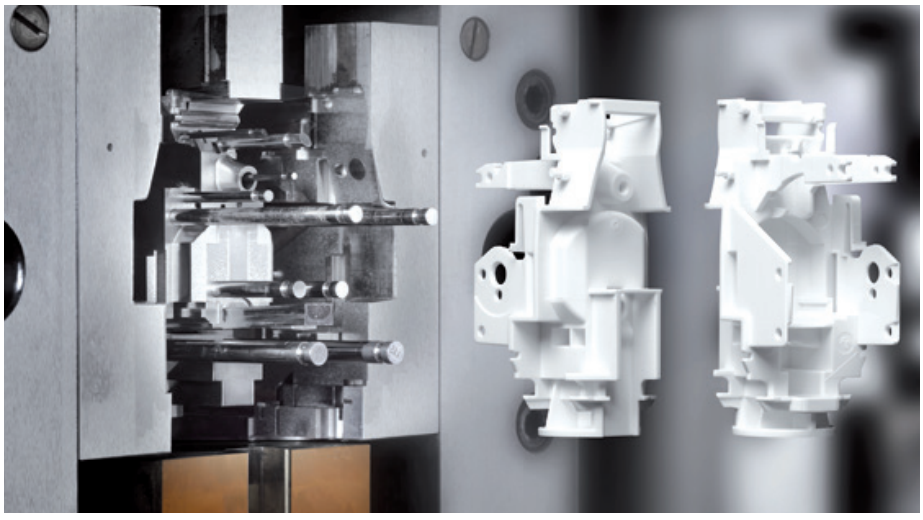


Figure 2: A hot runner mould.

for use in a cleanroom environment and ensures that 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 movable parts, as well as clean and material-appropriate part removal, achieved via inclined removal surfaces that avoid abrasion.

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

> "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."

Award-Winning Mould Making Department

The irrefutable quality of Gerresheimer's mould-making department was recognised by its top placement in the renowned "Excellence in Production" competition, which is organised by the Laboratory for Machine Tools (RWTH Aachen University, Germany) and the Fraunhofer Institute for Production Technology (Aachen, Germany). In 2014 the TCC of Gerresheimer Regensburg GmbH claimed first place to become "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 prove moulds to check performance and measure, optimise and qualify moulds. Moulds are sampled using special machinery under near-series conditions and are 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 setup 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. 4 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 (Figure 3), 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 are documented in an initial sample test report. The measurement equipment includes:

- Various multi-sensor coordinate measuring machines for optical and tactile component measurements
- Universal coordinate 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 material worldwide. The standard

Figure 3: Measuring lab in the Wackersdorf TCC.

Figure 4: Fully automatic assembly line in an ISO 14644-1 Class 8 cleanroom.

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 the 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. Mould qualifications are, however, time and cost intensive. This is why Gerresheimer offers its customers various mould qualification levels depending on the product, its area of application and regulatory requirement level.

AUTOMATION ENGINEERING

Together with the development and construction of the special-purpose machines associated with the moulds, Gerresheimer Medical Systems offers its customers high-performance automation solutions (Figure 4). In the pharmaceutical 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
- Specifies, designs, builds, procures and qualifies:
  - customer and parts-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.

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 cleanrooms in accordance with ISO 14644-1 Class 7/8 or GMP Grade C/D, globally standardised to a high quality level. Being an international manufacturer, Gerresheimer also monitors and assists the start-up of its production equipment on the customer's site.

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 in order to avoid the risk that they unknowingly don't have their medication available. 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 that Gerresheimer don't wait until mass production to develop automation solutions, but develop them in the prototype and pre-production phase, resulting in much time saved.

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, these

Figure 5: Small batch production includes its own measurement lab.

small batches may be required as clinical samples, development samples or stability batches. With its TCCs, Gerresheimer offers customers 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 (Figure 5). These facilities include the aforementioned Class 8 cleanroom and some of the injection moulding machines have integrated laminar flow covers to create a Class 7 cleanroom environment in the injection molding area. Project-specific assembly units and specific measuring technologies complete the equipment.

Expansion Into Glass

Gerresheimer is expanding its Wackersdorf TCC. The company is investing tens of millions in creating 3,000 square metres of additional space for the development and industrialisation of glass products, such as syringes and cartridges. The task area of the TCC is thus being expanded to include working with glass. Construction began recently, and the project should be completed by the end of the year.

One focus of the expansion is the establishement 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) in order to develop innovative technologies for glass forming and automation. In the future, new generations of glass forming lines for syringe production will originate in a cooperation 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.

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 a pharmaceutical small batch production. Additionally, Mr Wiglenda is Senior Director of Internal Tool Making.

CONCLUSION

Utilising the equipment and latest technologies in its TCCs, Gerresheimer is an expert pharmaceutical industrialisation partner. 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 highest-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.

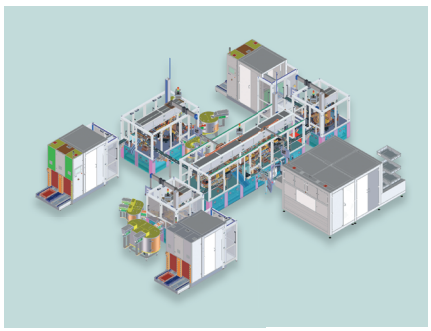
Deliver your active substance safely on target!

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.

Contract Development

Industrialization



Contract Manufacturing

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GERRESHEIMER

THE NEED FOR A RELIABLE SUPPLY-CHAIN & HOW TO CREATE IT STRATEGICALLY

Here, Antonio Teglia, Senior Director, Supply-Chain Management, and Devon McCrossin, Supply-Chain Leadership Program, both of Flex, discuss the increased importance of proper supply-chain management when it comes to mitigating the inherent production risks of today's increasingly complex drug delivery devices.

There are many impediments to drug delivery device companies aiming to successfully launch a new product. Amongst the most significant challenges are regulatory approvals, capital investments, clinical and market acceptance and, most recently, supply-chain reliability. For drug delivery devices, most of these challenges are impossible to predict, mitigate and risk-manage, with the exception of supply-chain reliability. Creating a reliable supply-chain is not rocket science, but it requires diligence, expertise and consideration early in the development process to influence the design of the drug delivery device.

> "Over the past 10-15 years, drug delivery device designs have come to vastly exceed those of their predecessors in terms of size, functionality and user-interface quality. These novel technologies represent significant supply-chain risks..."

REACTIONARY APPROACH

In the past, reliance on a reactionary approach to supply-chain risk management sufficed for the purchasing and manufacturing process of drug delivery devices, albeit at a higher expense. The devices used to consist solely of mechanical parts with limited electrical or connected abilities and no software. With few suppliers, wider quality tolerances and fewer process steps, the need to predict and manage supply-chain risk proactively was low.

Over the past 10-15 years, drug delivery device requirements have come to vastly exceed those of their predecessors in terms of size, functionality and user-interface quality. These novel technologies represent significant supply-chain risks and the increase in product complexity has, in turn, exponentially increased the number of components needed, and thus suppliers engaged. Most of the time, these expanded capabilities require the involvement of new, sole and/or single source suppliers with limited medical manufacturing experience. Additionally, the value chain used to consist of only a few steps to get the device from raw materials into the hands of the physician or patient, something which here is no longer the case.

The expanded number of process steps has broadened the geographical footprint of a device, adding yet another layer of risk to manage in the supply chain (Figure 1). When faced with the evolving global supply-chain network for drug delivery devices, the old strategy of reacting to supply-chain challenges as they arise is no longer effective. However, companies have been slow to implement proactive supply-chain risk management solutions.

Unfortunately, an increase in product recalls suggests that the drug delivery device industry overlooked critical risks. According to Stericycle, during the first half of 2018 the recall rate for drug delivery devices in the US increased 126% over 2017.[1] Manufacturing defects caused 94% of these recalls, specifically related to software and quality issues, out-of-specifications and more.

Another illustration of poor supply-chain risk-management techniques applied to drug delivery devices comes via the regulatory bodies. In the past five years, the US FDA increased the number of purchasing control violations issued to drug delivery device companies by 25%.[2] Most of these risks can be prevented with little investment by focusing on creating a robust and reliable supply chain during design. Regulatory bodies have started demanding more reliable supply-chain processes to grant approvals for new devices.

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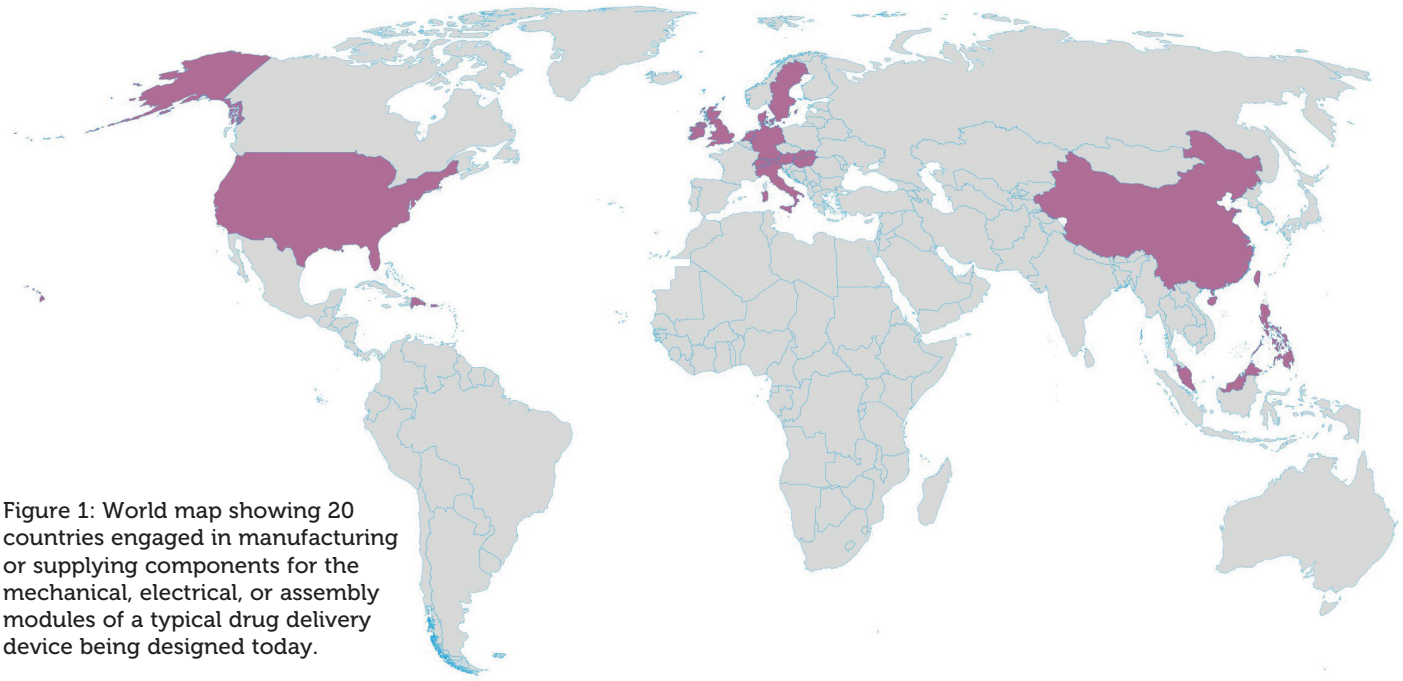

Figure 1: World map showing 20 countries engaged in manufacturing or supplying components for the mechanical, electrical, or assembly modules of a typical drug delivery device being designed today.

REGULATORY APPROVAL REQUIREMENT

Despite the number of FDA approved drug delivery devices increasing year over year since 2009, the requirements surrounding supply-chain risk management have become more detailed and effective.[3] The requirements for regulatory approval strongly align to the standards in ISO 13485 for the manufacturing of drug delivery devices. This standard was updated two years ago, in 2016, with increased emphasis and attention to supply-chain risk management. In fact, "risk" is mentioned 15 times throughout the standard and is mandatory to be considered for outsourcing and supplier controls.[4] The update reflects the fact that increased globalisation has caused organisations to operate more complex supply chains than in the past and, therefore, assume more risk in supplying consistently high-quality drug delivery devices.

INCREASING COMPLEXITY

As consumers more frequently demand the latest technologies, efficient user experiences and lower costs in their drug delivery devices, product complexity grows to meet the new market necessities (Figure 2 and Table 1).[5] Heightened product complexity without robust supply-chain risk-prevention procedures in place impacts time-to-market and total cost of goods sold, resulting in

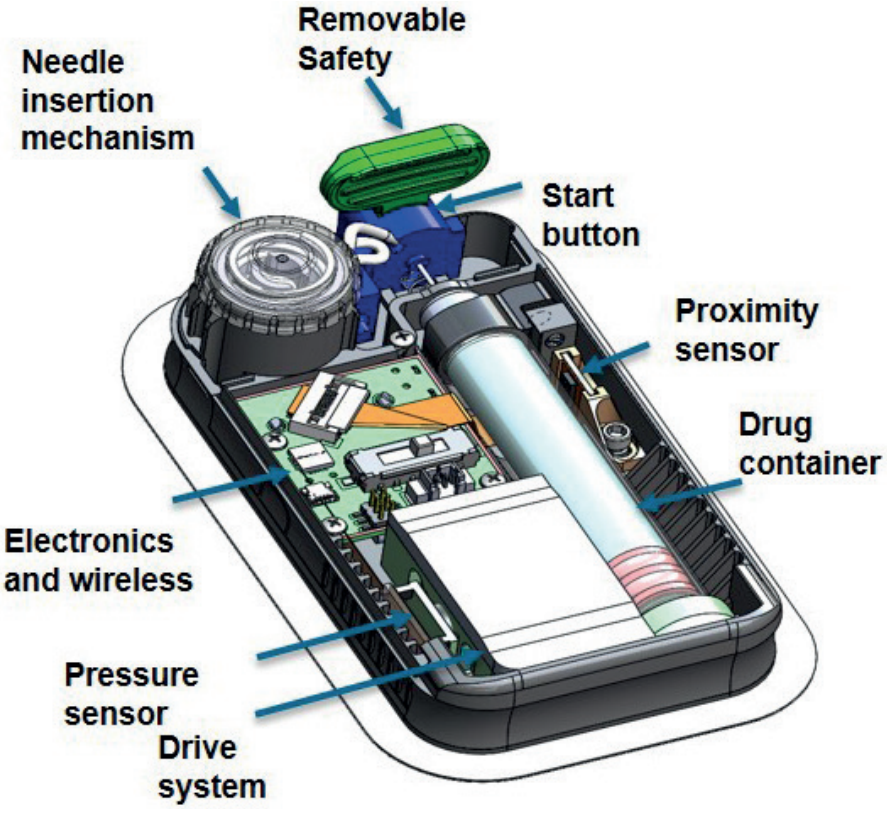

Figure 2: A reference design for a disposable patch pump highlighting the functionality and resulting design complexity of the drug delivery device.

Product Requirements
Automatic Needle Insertion
High Viscosity Drug Delivery
Standard 3 mL Glass Cartridge
Selectable Delivery Rate
End of Dose Detection
Bluetooth Wireless Connectivity
Haptic & LED Feedback
Low Cost
Light Weight
Low Profile
Disposable
Adhesion Strength & Comfort Balance
Sterile Fluid Path
Fluid Path Seal
Water-Resistance
One-Button Operation

Table 1: Product requirements and resulting drug delivery device design for a patch pump.

"To prevent supply-chain risks effectively, drug delivery device companies need to predict the highest risks to a product and implement risk management strategies accordingly during product design."

lost revenue and eroded product margin. For example, the worst-case scenario is when a critical, single-source supplier fails to perform during production, but the device has already been approved and launched. This can result in a product redesign, taking up to two to three years and US$10-20 million (£7.7-15.4 million).[6]

Emphasis on supply-chain risk prevention during the drug delivery device design phase can mitigate and reduce these impacts and improve agility. Controlling supplier quality and process is a clear action to prevent risk. However, with an increasing number of components, and consequently suppliers, drug delivery device companies cannot apply a blanket approach to risk prevention when it comes to sourcing. Products simply have too many suppliers and sub-suppliers to audit them all.

With over 150 components and 70 suppliers on a low-complexity device, how do you determine which suppliers and processes or sub-suppliers and sub-processes to audit and to what degree of scrutiny? A quantitative and qualitative risk analysis should be used to de-risk the supply chain during product design. Determining which suppliers present the highest risks draws on a combination of analytical tools, visualisations and continuous management.

RISK PREVENTION DURING DESIGN

To prevent supply-chain risks effectively, drug delivery device companies need to predict the highest risks to a product and implement risk management strategies accordingly during product design. In production, the ability to pivot as challenges arise depends on the degree of flexibility designed into the product and its supply chain. An analytical risk prevention strategy can predict which parts need alternatives, which suppliers require more management and which inventory management strategy should be applied to various components. Drug delivery device risk consists of three areas:

- Device safety
- Component functionality
- Supplier reliability.

Device safety is based on the FDA safety grade (high, medium, low), which impacts the requirements for filing and regulatory approval. Component functionality is determined by a technical engineering team through testing the feasibility of the components and device to perform as required. The resulting rating indicates the criticality (high or low) of each component in ensuring the proper functionality of the device. Both device safety and component functionality are consistent and accurate forms of measuring risk. However, supplier reliability, represented by a supplier's ability to meet demand on time whilst achieving consistently high-quality standards, is challenging to predict, measure and mitigate.

Sourcing, engineering and quality managers need to collaborate throughout the supplier selection process to address supplier reliability and highlight all potential sourcing risks. To adhere to budgetary and time constraints, a hierarchical strategy can be applied:

1. Measure the sourcing risk for each supplier based on quantifiable risk indicators, such as supply availability, customisation level, supplier relationship and time-to-recovery.
2. Assign each supplier to a risk level and apply varying degrees of supply-chain risk prevention and management to each category to optimise cost and time effectively.
3. Track and visually display the dependencies and intricacies of the total supply-chain as a system.
4. Update and re-evaluate continuously throughout drug delivery device design, introduction, growth, stability and end-of-life, pivoting strategies based on product requirements.

This high degree of supply-chain management is required to eliminate the risk of critical quality issues and product recalls during production. Addressing these factors early affords the engineering team the ability to change the drug delivery device design to mitigate business or supplier constraints before the design is tested and approved with the regulators. Addressing supply-chain reliability during design does not extend the timeline for development nor does it impact time-to-market expectations. Once production begins, it is too late to apply many risk prevention strategies, therefore acting early and predicting risk is the most effective and cost-conscious approach to handling the increasing complexity within the drug delivery device industry.

The last consideration for achieving a reliable supply chain is consistent supply-chain management. This requires a supply-chain manager to own the responsibility for the device's supply chain, starting

BOX 1: COMMON ABBREVIATIONS IN SUPPLY-CHAIN MANAGEMENT

Acronym	Definition
PCB(A)	Printed Circuit Board (Assembly)
EE Component	Electrical Component
SMT	Surface Mount Technology
ACF	Anisotropic Conductive Film
RM	Raw Materials
Tier 1 Supplier	Supplier of the Assembler
Tier 2 Supplier	Tier 1's Supplier = Assembler's Tier 2 Supplier

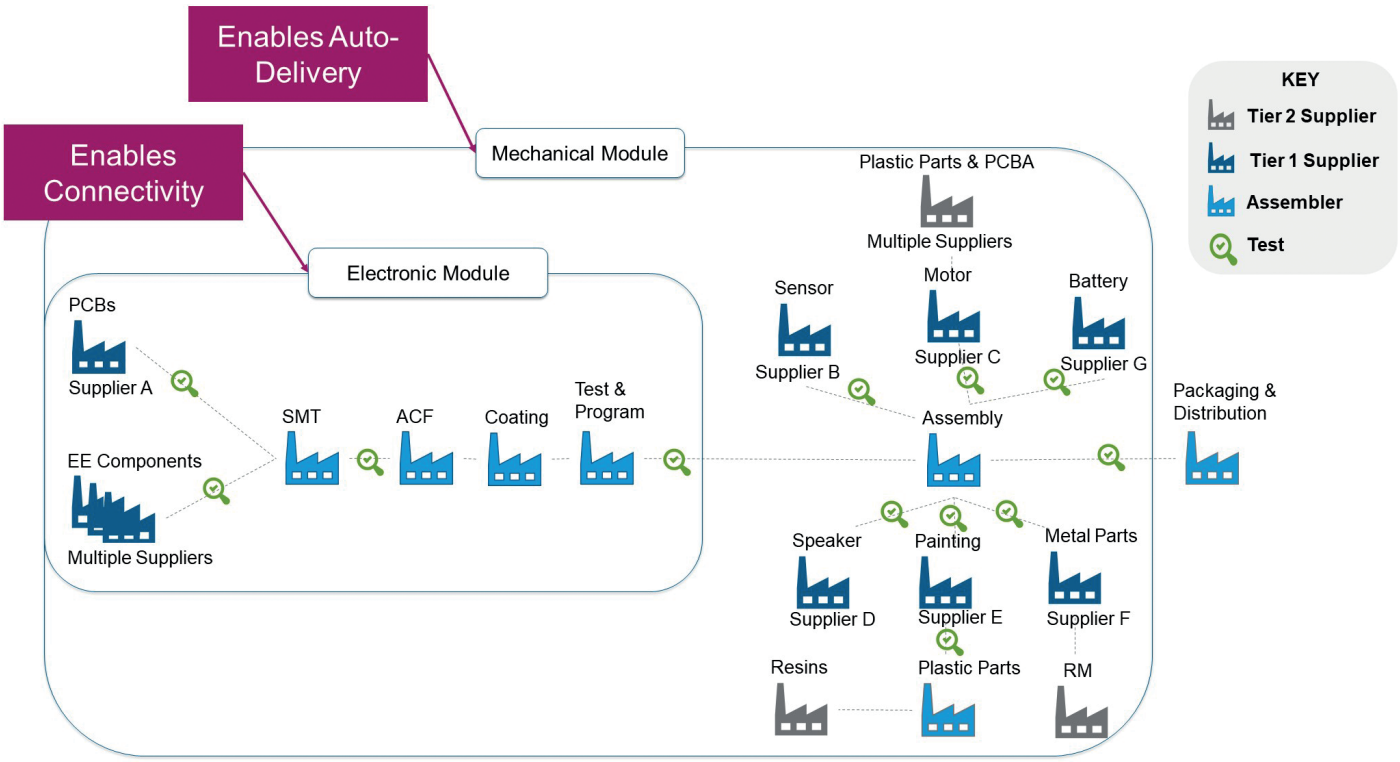

Figure 3: High-level overview of drug delivery device supply-chain.

from concept and continuing throughout the entire product lifecycle. This strategic manager can drive design decisions, engage with all stakeholders and easily pivot as issues arise in production through continued risk prevention actions.

CASE STUDY

Let us consider a disposable drug delivery device, designed in parallel and consisting of over 200 parts with 50 suppliers covering a geography of 22 countries.

Figure 3 shows the complexity within the drug delivery device supply chain and is related to the case study. It shows an overview of the delivery device's supply chain for the electronic and mechanical modules, including suppliers, sub-suppliers and value-add manufacturing process to keep in control, during production for just the device, excluding the disposable supply chain. The improved visibility enables accurate estimations of risk probability and impact, focusing supply-chain managers' time on the most critical risk prevention and mitigation actions.

Total Product Risk

The device, disposable components and suppliers were evaluated from the first concept phase. A potential supply risk emerged: low product forecast. The strategic supply-chain manager emphasised scouting and sourcing a catalogue for standard components above most other product design requirements from the customer. This reduced the material costs, allowing the customer to make a compelling business case for bringing the product to market at the development phase stage gate. Without early involvement of the supply-chain manager, giving them sufficient time to scout and negotiate with suppliers and internal teams, high material costs could have stopped production of the product all together.

Electrical Components

In the cyclical nature of the electronics market, supply capacity can become suddenly restricted, resulting in long lead times and high prices. Strategic supply-chain managers have increased visibility to market conditions and can suggest which components need alternatives tested and approved before product launch or ramp to ensure that lead times will not affect production schedules, resulting in lost revenue.

Custom Mechanical Components

Best practices dictate that total cost needs to be considered when selecting a custom mechanical component supplier. This leads to prioritising suppliers located near the final assembly location to reduce logistical costs. However, more risks need to be considered since these suppliers tend to be untested and small. Risks include, but are not limited to:

- Capacity flexibility to react to unstable forecasts of new drug delivery devices
- Investments necessary to activate a second source and audit the quality and process
- Disaster recovery plans
- Financial stability
- Complex process with unknown sub-suppliers.

For the drug delivery device described

above, custom mechanicals made up about a quarter of all components. The strategic supply-chain manager drove supplier selection through a quantitative supplier comparison and evaluation process, uncovered the highest risks and recommended mitigations in parallel to design activities, meeting tight time-to-market customer requirements and achieving a successful product launch and ramp.

ABOUT THE COMPANY

Flex is the Sketch-to-Scale™ solutions provider that partners with customers to innovate, design and build intelligent products in a connected world. With over 200,000 employees and 2,500 engineers across 30 countries, Flex can accelerate time to market and optimise resource allocation for efficient, cost-effective solutions throughout the product lifecycle. The Flex Health Solutions segment is FDA-registered and has ISO 13485 compliant facilities. Leveraging real-time supply-chain insight and advanced platform technologies across multiple industries, Flex provides opportunity for business growth in a smarter world.

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ABOUT THE AUTHORS

Antonio Teglia has an MS in Electrical Engineering and 20 years of experience in procurement and supply-chain management, specialising in drug delivery devices. He has extensive international experience working with suppliers and customers in Asia, Europe, and North America.

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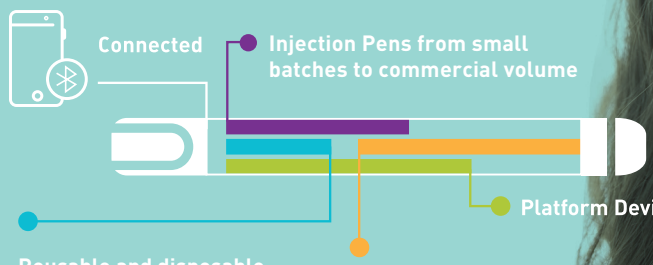
INNOVATIVE
PEN INJECTION SYSTEMS



HASELMEIER
Drug Delivery. Tailormade.

Pioneer of **Injection Pens** for subcutaneous application

Haselmeier: Solutions - from concept to series production

Tailored solutions for innovative medication delivery systems for subcutaneous self-application – that's Haselmeier. Specializing in small and medium volumes, the company is a development partner for pharmaceutical and biotechnology companies wanting to launch a new product on the market in a short period of time with efficient cost management. Haselmeier is an expert in injection pens and continuously works on new product innovations and designs that are at the highest level of technology and meet current regulatory requirements. As a reliable partner, we make an economic and timely market supply and customized access to personalized treatment possible.

The new D-Flex: new-generation medication delivery system

The D-Flex pen for modern personalized medicine

Individual solutions and custom treatments – modern medicine is increasingly focused on individual people and their needs. Haselmeier took this approach at an early stage and supports pharmaceutical manufacturers today with a pen that is more flexible than most other models on the market. Depending on the active ingredient and desired treatment, the D-Flex pen allows the patient to administer medication subcutaneously with a single fixed dose or with multiple fixed doses. Up to ten separate fixed doses can be delivered. What is particularly important for the patient's safety: the accidental use of interim doses is virtually impossible.

Connectivity creates new possibilities for improved treatment efficiency

Thanks to advanced medicines today, many illnesses can be treated so well that the patients can live an active lifestyle. This also includes patients taking more responsibility for themselves and their treatment. Equipped with modern medication delivery systems, they can always rely on their medical supply no matter where they are. Haselmeier is working on bringing innovative injection pens with Connectivity to market. For example, doctor, patient and relatives can be informed of dosage intervals, the application data and recommended dosage units can be transmitted, and medical devices can be monitored and controlled all using a smartphone.

From concept to scale with Haselmeier

As experts in injection-based self-medication, what sets Haselmeier apart is the reliability of its treatment, thanks to customized system solutions, and its scalability, convenience and intelligent control and monitoring. For more than 100 years, the experts at this family-run company have worked hard to develop high-quality injection systems for subcutaneous application.

Contact

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Innovation in Drug Delivery Platforms:
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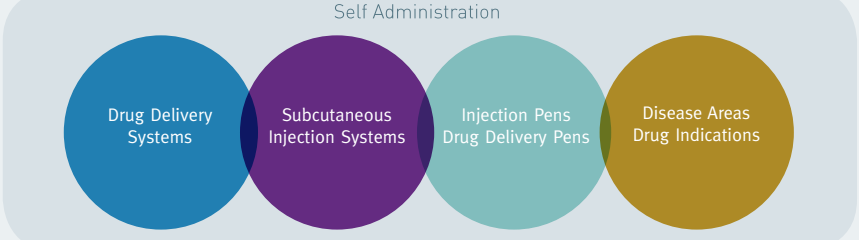

BEYOND MANUFACTURING: INDUSTRIALISATION OF DRUG DELIVERY IN THE REAL WORLD

When discussing the industrialisation of drug delivery, it is natural to focus on the processes and management of manufacture. Here, Napoleon Monroe, Managing Director, New Directions Technology Consulting, provides a different perspective on the idea of drug delivery's "Industrialisation" and what that might mean in the modern world of service industry.

The industrialisation of drug delivery extends well beyond the research lab and production facility. Healthcare, including pharma in the US and elsewhere, is being driven by forces, developments and complexities beyond the control of the legacy stakeholders. This article provides an overview of a wave of industrialisation sweeping over the pharma sector. Some aspects of these changes present opportunities, some are highly problematic. The observations discussed herein may relate as well to research and pharma manufacturing, however, while wide-ranging, this article is not all-inclusive.

> "Drug delivery is not the same industry as it was just a few years ago when the manufacturers' supply chain essentially ended with a product being delivered to another company."

THE DRUG DELIVERY INDUSTRY

Drug delivery is already an industry, albeit a fragmented one, with many stakeholders (see Box 1). It is an industry that often takes on different forms between one situation and the next. For example, drug delivery is not the same industry as it was just a few years ago when the manufacturers' supply chain essentially ended with a product being delivered to another company. Now in drug delivery, the patient is commonly regarded as the end-point. Drug delivery is changing to include lessons, realities, techniques and concerns from other industries. The industrialisation of drug delivery has brought progress but, in some ways, there is still more promise than progress. Like it or not change has, and will continue to, come. The challenge is: How do we humanise industrialisation to better benefit patients, other stakeholders and society?

> "The big tech companies, such as Amazon, Apple and Google, "get" these consumer desires, building success off the desire for instant information."

PRACTITIONERS AND HEALTHCARE SYSTEMS

Many years ago, doctors compounded and delivered patient-specific medications themselves on a case-by-case basis, with far fewer products, none biotech, to consider. Injections, except insulin, were given in the office. This is simply no longer the case.

Many practitioners express a preference for the "good ol' days" when their decisions were not challenged by the new norms and complexities inherent to the modern healthcare industry. When they did not have to rely on staff, managers and computers to practise medicine. When they could give a low-income patient, who could not afford an autoinjector, a syringe and a vial of epinephrine without fear. They wish they did not have to waste time on badly designed medication reconciliations in electronic medical records (EMRs) and complex billing codes. There were few expectations for service and support for patients until the next office visit or house call.

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Pharma's customers were the MD decision-makers in individual practices. Until rather recently, practitioners relied on approvals from clinical trial data and what pharma representatives told them.

Nowadays, patient centricity has become a healthcare mantra. Professional specialisation and drug delivery by non-MDs, including patients themselves, have changed drug delivery and disposal requirements. Healthcare organisations track re-admissions and follow cases into the real world over time. Healthcare mergers and acquisitions both within and outside pharma have changed the decision-making process for drugs and drug delivery. Product performance evaluations are becoming part of healthcare provider and payer value models. Purchasing decisions are more made by non-MD general and materials management professionals and are based on proven relative product value. Payment for outcomes is becoming a reality. Pharmacy benefit managers and other stakeholders have inserted themselves into the decision and reimbursement processes.

Practitioners and staff now often work for corporations. Clinicians are overwhelmed with raw data, which is not parsed into useful information. Professional interactions are timed, as are the activities of production line workers. Models from other industries such as the checklists used in aviation and the Toyota Production System are now part of healthcare best practices.[1,2]

CONSUMERS, AKA PATIENTS

Until somewhat recently, patients were relatively uninformed about the drugs that they were prescribed. For most insured patients, drug costs were not a significant factor. However, patients are now required to pay a greater share of their pharma expense. This drives a greater desire for pharma information, leading to the situation now where pharma has to increasingly deal with patient/payers who have come to expect instant gratification of their desire for product information.

The big tech companies, such as Amazon, Apple and Google, "get" these consumer desires, building success off the desire for instant information. Amazon's subscription model, one-click ordering, preferred product selections, verified purchase reviews, personal order history and "customers also bought" features; Apple's Genius Bar; and Google's assisted intelligence have changed the retail, publishing and search industries.

BOX 1: STAKEHOLDERS IN THE COMPLEX DRUG DELIVERY INDUSTRY

- Patients
- Payers (patients (again), taxpayers (again), government entities, true insurers (patients, National Health, Veterans Administration, Medicare, Medicaid, employer plan sponsors), some other insurers (companies that mainly administrate and negotiate, only paying after certain conditions have been fulfilled, e.g. after plan limits have been reached)
- Regulators
- Legislators and voters
- Pharma manufacturers and their CROs, CMOs, API and excipient suppliers, and venture partners
- Stockholders and financiers
- Insurance administrators and brokers
- Combination products manufacturers and their component manufacturers and processors
- Medical practitioners including pharmacists
- Distributors and marketers, including wholesale, retail and pharmacy benefit managers (PBMs).
- Consultants, lobbyists, media, publishing and advertising interests
- Politicians, especially legislators and governmental officials
- Patient advocacy groups
- Professional and trade associations
- Standards development organisations
- Data carriers, analysts and aggregators
- Academics
- Litigators
- Others

NOTE: Employers, employees, families, caregivers, contractors, lobbyists, consultants and even friends of all of the above. Interrelationships and ranking of importance change situationally issue-by-issue.

These companies and others assist their customers and use their informatic tools to extend the functionalities of their supply chains to end-users and other stakeholders.

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

CHANGES FOR OTHER STAKEHOLDERS

The pharma product mix and consolidations at pharma-related companies have changed drug delivery. Specialty pharma products are usually expensive and require more care and supporting information. Many are injectable and are delivered outside institutional settings. Specialty pharma, especially biotech, has become the leading revenue source for the pharma sector, with the age of the "blockbuster" drug product clearly waning. Products of the much touted "personalised pharma" concept follow the specialty pharma model.

Consolidations in and around drug delivery provide economies of scale and enable the adoption of technologies developed in other industries. Specialisation around diseases and mergers, such as that of Express Scripts and the insurer Cigna, are examples of growing scale and cross-industry consolidation. Some pharma stakeholders have been reluctant to adjust to some of these changing industrial realities.

ADVANCES IN DIGITISATION

Consumer retail long ago adopted the EAN/UPC barcode in advance of any governmental requirements. Only since 2013 have drugs and medical devices seen the introduction of standardised automated identity and data capture systems (AIDC), including barcoding and serialisation, for pharmaceuticals, devices and combination

"Retail booksellers were quite complacent when Amazon first began selling books in 1995. Drug delivery companies are now trying to avoid a similar disruption."

products. The US Drug Supply Chain Security Act (DSCSA) and the Unique Device Identifier (UDI) regulations were largely proposed in response to the desire to rid the supply chain of unapproved, counterfeit, illegally diverted and recalled products.

Beyond these objectives, AIDC gives healthcare a language for gathering other information and allows automation of information collection. The common language feeds "big data", allows for aggregation, facilitates analysis and can bring greater transparency.

Financial information, such as pricing, is not part of the US DSCSA and UDI. However, standard nomenclatures, as seen in databases related to these programmes, can be used as a means for gathering financial information. Pan European Public Procurement Online (PEPPOL) is used in some UK trusts and elsewhere to gather pricing and other information beyond the scope of the US regulations. Some non-governmental organisations (NGOs), including some for-profit organisations, are also aggregating information beyond the regulatory requirements. Healthcare specialities are moving toward standard diagnosis, treatment and adverse effect codes across professions.[3] In the US, even in the absence of a national health system, stakeholders are pushing toward EMR interoperability.[4]

AUTOMATION AND TELECOMMUNICATIONS

There are now internet-connected refrigerators, doorbells, toothbrushes and many other such connected "things". It should be no surprise then that automation and telecommunications continue to penetrate healthcare and, specifically, drug delivery. For example, automated "robo-call" medication refill reminders are commonplace. Connected autoinjectors are on the market and, with a new strap, an Apple Watch can be made into an electrocardiogram (ECG/EKG).[5] Standards are in place for regulatory-compliant data transmission.

As in other industries, the range and number of internet-connected healthcare "things" continues to grow, adapting applications, sensor, power and analytical means from other industries. Because of the importance of pharma regimen compliance, vital signs monitoring and the human factors which can impact drug delivery, these connected healthcare "things" are more useful in meeting real needs than some connected "things" in other industries.

DISRUPTION

Retail booksellers were quite complacent when Amazon first began selling books in 1995. Drug delivery companies are now trying to avoid a similar disruption, with new entrants and combinations in drug delivery worrying legacy stakeholders. Examples abound:

1) Amazon buys PillPack and introduces an over-the-counter pharma line.
2) CVS buys Aetna.
3) Apple re-enters healthcare with Apple Health.
4) Berkshire, Amazon and JP Morgan appoint Dr Atul Gawande as CEO of their newly formed healthcare company.

Publicly listed pharmacy companies took a hit to their stock on the day Amazon announced the PillPack purchase. Combinations are one response by legacy companies.

DEPENDENCIES FOR SERVICES AND DEVICES BEYOND MANUFACTURING

Years ago, there was little demand for "service beyond the pill" and little pharma interest in supplying it. Most pharma companies were not traditionally very engaged in home-use delivery systems beyond oral solids and liquids, topicals and sprays. Indeed, pharma still often relies on contractors to design and manufacture delivery devices. These devices and their component providers are often offshore and rely on standards such as ISO 13485.

"Devices and services from non-pharma companies have become part of a landscape of the drug delivery industry, thereby further pushing the drug delivery industry past just research and manufacture."

Pharma relies on pharmacists and others to assist with providing service. Pharmacists have been expanding their roles since the beginning of the generic movement. Beginning with the biotech revolution, pharmacy benefit managers and specialty pharmacies are coming to have larger roles.

Pharma, practitioners and patients are somewhat co-dependent in reporting medical effects, behaviours and compliance with the pharma regimen. Contract outsourcing and assisting patients have added layers of responsibility to the pharma industry. Devices and services from non-pharma companies have become part of a landscape of the drug delivery industry, thereby further pushing the drug delivery industry past just research and manufacture towards being a fully-fledged globalised service industry.

The relatively new (2002), US FDA Office of Combination Products works to bridge the regulatory gaps between pharma, software and device industries. These industries, and human factors professionals, are industrialising drug delivery supply chains to extend to the patient wherever and whomever they may be.

INTERNATIONAL STANDARDS AND REGULATORS

US companies have often lagged behind in the standards-setting process. In the US, ISO and other international standards were, and largely still are, "voluntary". The reality is that more regulators, and other stakeholders, in the US and elsewhere are relying on international standards. Such, increasing reliance impacts timing for regulatory approvals, cost, litigation defence, marketing plans and return on investment (ROI).

Quality systems audits that help ensure that planes don't fall from the sky because of component or systems failures are already in place in the aircraft industry. Aircraft parts are customarily serialised, tracked and traced. The Aviation Suppliers Association, working with the International Accreditation Forum (IAF), helps manage

such a system for the aircraft and other industries. Some industries have agreed to audit databases so that stakeholders can rely on audit certificates.

Neither drug delivery companies nor their regulators can effectively audit the quality systems of everyone supplying components and finished products into the US. The IAF has proposed a registry system for valid ISO 13485, the Medical Device Quality Standard. Also, some regulators are working to implement a new Medical Device Single Audit Program (MDSAP).

ABOUT THE AUTHOR

Napoleon Monroe, Managing Director of New Directions Technology Consulting, has a diversified background that extends from developing and producing emergency pharmaceutical delivery systems to managing private brands for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes as business opportunities, risk management and international marketing, with experience managing business relationships in more than 30 countries. Mr Monroe has led teams that have invented and commercialised major products, such as EpiPen and ATNAA.

Success in randomised clinical trials is being augmented, even supplanted, by real world evidence. Regulators' drug adverse event and medical device reporting systems are being supplemented by the FDA's National Evaluation System for (medical) Technology (NEST), which can trawl the internet to capture patient experiences.

THE REALPOLITIK SURROUNDING PHARMA AND DRUG DELIVERY

Legislative and regulatory discussions surrounding drugs and drug delivery are loud and fractious. Ethical lapses and erroneous assumptions highlighted by the media pose a high risk of generating anger among stakeholders. The pharma pricing model in the US was, and still is, quite opaque. Legislative and regulatory pressure on rebate systems and pricing is building. Globalisation continues to be a factor, especially in multinational pharma companies.

While there are economies of scale for regulatory harmonisation, regulatory nationalism is now more of a factor, for example China has a different standard for barcodes and country-specific symbol and language requirements seem to be becoming more prevalent. With an eye on digitisation, data ownership and security are issues for real world data collection, with various governments introducing or looking to introduce new, stronger data laws, such as the EU's General Date Protection Regulation (GDPR).

SUMMARY

The factors discussed in this article have changed other industries. The drug delivery, pharma and related stakeholder industries are engaged in change management exercises. The magnitude of what they are trying to manage can be seen when one examines changes wrought in other industries. To quote Sam Cooke:

"…I know a change gonna come…"

This article reflects the author's personal opinions and analysis. It is not a professional interpretation of any medical, regulatory or legal requirements. The author, the licensees to his intellectual property and his clients have interests in healthcare with a focus on medication telemanagement.

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DEVICE MANUFACTURING FROM DEVELOPMENT THROUGH COMMERCIALISATION

In this article, Sheleagh Dougan, Business Development Manager, and Meredith Canty, Director Drug Delivery Systems, both of SMC Ltd., give an overview of the scales of manufacturing throughout the design of a new combination product and the necessary considerations at each one.

This article is based on an SMC Ltd. white paper: "Insights Into Drug Delivery Device Manufacturing From Development Through Commercialization".

INTRODUCTION

Over the past decade, the pharmaceutical industry has witnessed the emergence of biologics and targeted therapies, resulting in abundant opportunities for pharma companies. With technological advancements and a greater understanding of effective treatment options, novel delivery methods are being introduced, giving pharma companies a competitive edge and offering patients better solutions for their needs.

For drug delivery device engineers, this opens up opportunities to design innovative device solutions that meet both the needs of these new formulations and their target patient demographics. Prefilled syringes remain a viable option for applications administered by healthcare professionals. Patients who self-inject are faced with various challenges, often due to the very disease they are managing, such as limited joint mobility from rheumatoid arthritis, vision limitations from migraines or the stress of administration in an emergency situation. As such, sophisticated patient-centric devices are being introduced and embraced.

> "In the past, pharma has viewed the drug delivery device as a secondary concern. It is easy to understand this since many drug delivery devices are, by definition, secondary packaging."

In the past, pharma has viewed the drug delivery device as a secondary concern. This way of thinking is easy to understand since many drug delivery devices are, by definition, secondary packaging. This approach often left little-to-no time to develop the optimal drug delivery solution for the patient. Device engineers were forced to use existing technologies to meet the established timelines, which in turn resulted in less-than-ideal device solutions. Pharma has since recognised this as an issue and is changing to include device teams in early stages of drug development. This allows the team appropriate time to design and develop an optimal delivery method to meet the needs of the patient as well as the needs of the formulation.

When developing a combination product, a greater opportunity for success exists when the device technology is optimised to meet the patient and stakeholder needs. When those needs cannot be met with an existing platform, selecting a knowledgeable team with the design, development, regulatory and manufacturing knowledge to meet the requirements results in a robust device design with greater chance of successfully launching in the market.

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Manufacturing Finished Devices From Concept To Completion

Product Development

- Design for Manufacturability (DFM)
- Risk management and FMEA
- Develop pilot manufacturing
- Producting testing development
- Supplier sourcing and qualification
- Manufacture devices for:
  - Engineering testing
  - Human factors studies
  - Usability testing
  - Design verification testing

Clinical Trial Manufacturing

- Manufacture clinical trial devices
- Process validation (IQ/OQ/PQ)
- Regulatory documentation support
- Commercialisation planning
- Supply chain management
- Finalise:
  - Product specifications
  - Functional testing
  - Design freeze
  - Packaging and Labeling

Commercial Manufacturing

- FDA pre-approval inspection
- Manufacture launch quantities
- Regulatory approval
- Customer product release review
- Product life cycle management
- Scalable manufacturing:
  - Launch with pilot solution
  - Increase capacity to forecast
  - Implement semi-auto solution
  - Implement fully-auto solution

Figure 1: Considerations at each scale of manufacturing prior to product launch.

The capabilities needed to evolve a drug delivery device from product development through commercial manufacturing are shown in Figure 1. Whether pharma companies outsource some or all of these phases, the device team must plan accordingly for product development, clinical trial manufacturing and commercial manufacturing. An overview of each of these phases follows.

PRODUCT DEVELOPMENT

During formulation development, the pharma company will determine the best device path forward with either a novel device technology or a modification to an existing device platform. Whether the device team is located within the pharmaceutical company or contracted to a product development consultancy, it is important to engage the device manufacturing partner at this stage. This ensures that the device is optimised for manufacturability at the projected commercial product volumes within the expected bounds for timeline, device quality and financial requirements.

The device manufacturing partner should provide significant input on the device design. Analysing the device from the tooling, moulding, assembly, automation and testing perspectives, ensures that the design and manufacturing methods are robust for long-term manufacturing. The manufacturer should also provide the pharmaceutical company with scale-up plans for the device, including the risks and benefits associated with each phase of the product lifecycle. Part of this process includes understanding the device specifications and reviewing the design failure mode effects analysis (dFMEA). Understanding what is critical from a design perspective allows the device manufacturer to create manufacturing solutions that de-risk the manufacturing process.

The device manufacturing partner should propose the best path forward from a tooling and assembly perspective. The manufacturer should initiate a process failure mode effects analysis (pFMEA) to identify and prevent as many risks as possible. The pFMEA should be reviewed by both the manufacturer and the pharma company to ensure all parties understand the areas of risk. If there are areas that have too much risk, a review will determine possible solutions to reduce it. Identifying risks early allows for the planning of risk mitigation solutions to create balance between risk, cost and timeline. The device manufacturing partner should utilise these analyses to fabricate pilot tooling and equipment to manufacture devices for product testing development, human factors studies, design verification testing, stability testing and other requirements for development.

"The device manufacturing partner should provide significant input on the device design. Analysing the device from the tooling, moulding, assembly, automation and testing perspectives, ensures that the design and manufacturing methods are robust for long-term manufacturing."

CLINICAL TRIAL MANUFACTURING

Prior to obtaining regulatory approval for a combination product, several phases of clinical trials must be performed to collect the requisite safety and efficacy data. Due to the high cost of clinical trials and the length of time to complete all phases, it is critical to have high quality, fully-functional devices available for the clinical trial. This can be achieved by partnering with a device manufacturer that has the necessary quality systems, including US FDA 21 CFR Part 4 compliance. Being Part 4 compliant allows the device manufacturer to handle and integrate the drug product, then perform the final combination product assembly, labelling and packaging. By utilising a single source to manufacture the combination product, a pharma company can reduce risk and cost, and put their focus on preparing and executing the clinical trials.

Clinical trial manufacturing should be discussed during the product development phase. The device manufacturer should provide a robust solution to develop a device that is capable of meeting clinical trial low-volume, high-quality requirements. When reviewing the pFMEA, it must be considered that the device could be for human use at this phase, therefore risks must

be mitigated and controls must be in place. Examples of risk mitigation controls are proper pack-out configuration of components or implementing 100% inspection of a critical specification during assembly.

COMMERCIAL MANUFACTURING

It is important to start planning for commercialisation as the combination product advances through each clinical trial phase to ensure the device is as robust as possible, risks have been properly mitigated and a manufacturing plan has been put in place to ensure that the tools and automation can achieve the projected volumes. Depending on the commercial manufacturing solution, the timeline to develop, design, build, test and validate new tools and automation can exceed a year. The timeline and budget must be discussed early in the programme to ensure all parties agree on a commercial manufacturing path and the point in time at which the plan will be initiated.

A critical decision for combination products is the location for manufacturing, labelling and packaging. If the decision is to outsource this activity to the device manufacturing partner, all preparations for the FDA pre-approval inspection must be initiated as early as possible. All quality systems must be appropriately updated, validation activities made robust and an internal audit conducted to review and address any gaps prior to the FDA audit.

Another critical component is the launch strategy. When developing a commercial launch strategy there are multiple factors to consider including device specifications, projected annual volumes, timeline, capital budget and target selling price. Launching the product as soon as practical after regulatory approval provides both market and financial benefits. This ideal situation can be achieved by launching with the validated pilot tools, equipment and processes utilised for engineering and clinical manufacturing. A thorough pFMEA should be conducted and reviewed together with the pharma company so that all parties understand the benefits and risks associated with launching with this strategy. Although the capacity of the initial manufacturing line may not meet the needs for future product growth, the device contract manufacturer can utilise the knowledge gained during the device development and plan ahead to provide manufacturing options to meet the quality, forecasted volume and economic targets throughout the lifecycle of the product.

"Launching the product as soon as practical after regulatory approval provides both market and financial benefits. This ideal situation can be achieved by launching with the validated pilot tools, equipment and processes utilised for engineering and clinical manufacturing."

SUMMARY

Biologics and other targeted therapies often require low annual volumes, however the device manufacturing strategy must still fit commercial expectations. Optimal manufacturing solutions should be identified to meet the quality, financial, timeline and patient needs of the product.

Including the device manufacturing partner as an early member of the device team provides important input to ensure that the device is designed for long-term robust manufacturing, risks to the product and processes have been mitigated and that a phased approach manufacturing plan is used. A launch strategy that takes into account the device specifications, projected annual volumes, timeline, capital budget and target selling price ensures the pharmaceutical company's targets are achieved and the device launches successfully. Finding the right manufacturing partner greatly improves the likelihood of this success.

ABOUT THE COMPANY

SMC Ltd. provides contract manufacturing of single-use devices for the healthcare, pharmaceutical and diagnostics industries. Dedicated to medical manufacturing, SMC provides full product services from initial concept through final packaged device including: programme management, design and development, product manufacturing, clinical manufacturing, electronics integration and global supply chain management.

ABOUT THE AUTHORS

Sheleagh Dougan, Business Development Manager, SMC Ltd., has over 20 years of experience in the healthcare manufacturing industry. She has worked on the development and commercialisation of life-saving combination products in both programme management and business development roles. Currently, Ms Dougan is leading the effort of developing new business opportunities in the drug delivery market through new and existing customer relationships.

Meredith Canty, Director of Drug Delivery Systems, SMC Ltd., has over 20 years of experience in the drug delivery space from a contract manufacturing perspective. Ms Canty has worked with many pharmaceutical companies, design firms and manufacturers to launch new drug delivery devices. Her experience ranges from managing the launch of new drug delivery combination products to increasing capacity on an existing product line by more than 50 million devices per year.

DRUG DELIVERY DEVICE MANUFACTURING

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THE CHALLENGES OF MANUFACTURING COMBINATION COMPONENTS

In this article Bob Parsons, Vice-President, Quality & Regulatory Affairs, and Jim Arps, PhD, Director, Business Development, both of ProMed Pharma, discuss three significant challenges faced by companies looking to manufacture components for combination products in the medical sector and how ProMed has risen to meet them.

This article is adapted from a set of ProMed Pharma LLC white papers: "The Challenges of Manufacturing Combination Components" Parts 1 & 2.

THE FIRST CHALLENGE – FACILITY DESIGN

In order to ensure that any new operation in a manufacturing facility will be sustainable, it is necessary to thoroughly evaluate and specify the intended production area's size, layout, equipment, utilities and safety precautions prior to bringing a new drug substance into the facility. Adequate space is required for receipt, segregation, handling, storage and testing of drug substances and other raw materials.

Drug substances must be received, quarantined, sampled, tested and released prior to use, all of which must then be documented. Each shipment is tested at a minimum for identity, however purity, strength and quality must also be confirmed, as later discussed. ProMed quarantines all incoming product in appropriate temperature, light and humidity conditions using monitored, temperature controlled cages, coolers and freezers. To help ensure released and unreleased materials are never mixed up, materials are labelled and their containers physically segregated.

The equipment, air handling, process flow, customer requirements, cleanroom layout and utilities must all also be considered during establishment of a new pharma production facility. For utilities, the actual daily consumption and demand are measured, and the quality reviewed. In cases where the utility has an impact upon product quality, directly or indirectly, validation testing is performed to verify quality. For example, ProMed uses compressed air to drive actuators and remove materials. In some cases, the compressed air is in contact with product and therefore needs to be validated to ensure that no oils, moisture or microbial contaminants are present.

To minimise mix-up and contamination, the equipment placement, processes, material and personnel flows are considered with respect to each new facility and appropriate process are implemented. Equipment and process requirements are evaluated for appropriate size, required utilities,

> "As each new manufacturing facility is brought online, ProMed performs design qualification to ensure the cleanroom suite has been built to both its and its customer's specifications."

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"As parts pass through a particular operation, data is recorded on the batch as a whole. However, in combination component manufacturing, there are processing steps where some characteristics of individual units are tracked."

construction materials and monitoring instrumentation. New equipment is qualified to ensure that it is suitable to meet process requirements and tolerance specifications. Measurement and testing equipment requirements are also evaluated and new test instrumentation is qualified for its intended use.

ProMed's typical pharma production facility is an ISO Class 7 cleanroom suite dedicated to a single customer (Figure 1). ProMed prefers to build its cleanroom suites with one or more air handler units, that serve the main manufacturing areas and the mixing rooms. The dedicated unit helps to ensure drug particulates generated during the mixing process are not recirculated into the main cleanroom. Additionally, the mix room is designed to have a negative pressure differential with respect to adjacent rooms, to further ensure that particulates don't escape.

As each new manufacturing facility is brought online, ProMed performs design qualification (DQ) to ensure the cleanroom suite has been built to both its and its customer's specifications. Once the facility has been initially qualified, an environmental monitoring programme is established. The new cleanroom suite is thoroughly cleaned, after which initial testing includes two three consecutive day periods, first with no operators present (static testing), second with operators present (dynamic testing). The airborne viable micro-organism, surface micro-organism and non-viable particulate

Figure 1: A ProMed Pharma production floor.

levels from this initial testing are used to establish a baseline and the initial alert and action levels. The facility is then added to ProMed's routine environmental monitoring (EM) programme and sampling is performed quarterly.

THE SECOND CHALLENGE – RESOURCES

Individual Component Versus Batch Processing

In much of the medical contract-manufacturing industry, the work order is the batch size, corresponding to a number of components processed through the manufacturing environment. As parts pass through a particular operation, data is recorded on the batch as a whole. However, in combination product component manufacturing, there are processing steps where some characteristics (e.g. weight, yield) of individual units are tracked. This is done to ensure that the correct amount of drug is incorporated into the manufactured component. ProMed uses a unit manufacturing process, however it also tracks individual components within each batch as necessary.

"Some organisations that are manufacturing combination products are actually moving towards performing personality profile testing on both existing and prospective employees to minimise turnover and error risk."

Conveyance Methods

Maintaining a unique part identity through several processing steps requires a conveyance method that is easy to use and capable of maintaining said individual part identity. For example, if a step processes 8 parts, then the part trays need to have 8 columns. This can also involve the use of placeholders. Throughout the process, rejected parts lead to empty spaces in the conveyance, thus placeholders are needed to ensure another part is not inadvertently placed in this location. If an acceptable part is placed into the wrong conveyance location the data from previous processing steps proving the part meets specifications are lost and, as a result, an acceptable part would be rejected.

Required Paperwork

Everyone in the medical contract manufacturing industry understands the importance of accurate device history records and other processing paperwork. Combination products impose a further level of required diligence. There is more of it, at times it can seem to be more confusing, and it subject to a higher degree of scrutiny. Paperwork errors can result in significant unplanned financial and delivery issues.

It takes a certain type of operator to perform successfully in this environment, especially when compared with other, less risky, roles. Some organisations that are manufacturing combination products are actually moving towards performing personality profile testing on both existing and prospective employees to minimise turnover and error risk.

Understanding Value

Combination product components are of the highest value of any of the parts ProMed presently manufacture (Figure 2). The addition of the drug, the additional processing data (individual units) and the higher requirements of the quality system all add cost. Additional time was spent with the operators so that they properly understood the impact of their actions when operations were not correctly followed, leading to scrap. Additionally, scrap from this type of operation is considered a hazardous waste and must be treated as such, resulting in further additional cost.

THE THIRD CHALLENGE – REGULATION

Up until recently, companies manufacturing combination products were faced with the formidable task of deciding how to best comply with multiple, and sometimes overlapping, regulations for both devices and pharmaceutical products. When the US FDA issued the final rule for 21 CFR Part 4, cGMP Regulation of Combination Products, on January 22, 2013 and the Final Guidance for Industry on how to comply with these new requirements in January 2017, much of the grey and conflicting areas were resolved, making it apparent that a either a device-based quality system or a pharma-based quality system, enhanced with supplementary policies and procedures to cover the other, is the preferred route.

ProMed's combination products quality management system (QMS) was derived from the existing ISO 13485 certified and 21 CFR 820 compliant device quality system used in its moulded products area. The key provisions of the Pharma regulations in 21 CFR 210 and 211 that are needed for manufacturing devices with a drug constituent are identified in Table 1.

Drug Product Containers & Closures

To comply with the additional pharmaceutical requirements, ProMed enhanced its pharma QMS to ensure that drug components and drug product containers are received using approved in-house procedures. Where cleanliness is a requirement, ProMed ensures cleaning of the containers and components takes place and that containers are closed and only opened in environmentally controlled areas to prevent the introduction of contaminants into the products or components.

Figure 2: Combination product components, such as these various cardiac pacing components to be loaded with a steroid, are very high value products.

Section	Description
Section 211.84	Testing and approval or rejection of components, drug product containers, and closures.
Section 211.103	Calculation of Yield
Section 211.132	Tamper-evident packaging
Section 211.137	Expiration Dating
Section 211.165	Testing and Release for Distribution
Section 211.166	Stability Testing
Section 211.167	Special Testing Requirements
Section 211.170	Reserve Samples

Table 1: Further regulatory requirements for manufacturing medical combination products.

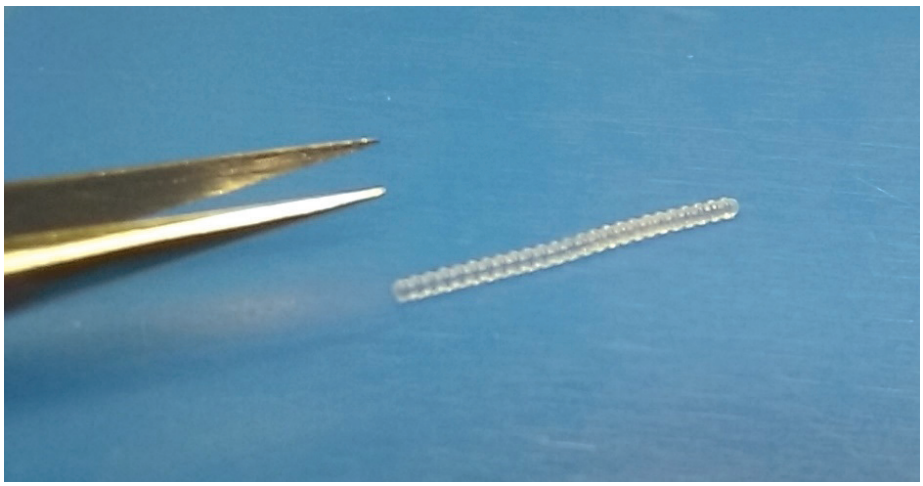

Figure 3: A moulded resorbable polymer implant for subcutaneous drug delivery.

Representative samples of each shipment of each lot are collected for testing. Certificates of analysis (CofA) are reviewed for compliance to pre-established materials specifications. If testing is required, the quantity of material and amount required for reserve samples is determined and sampled from incoming containers. Sampling is generally based upon the $\sqrt{N+1}$ rule for N number of containers unless a higher

"Once an API is fully encapsulated within a silicone matrix through the moulding processes, the next step is to confirm the drug's elution profile and burst. In other words, we test and confirm how fast the drug substance elutes or discharges from the silicone."

degree of scrutiny is required. Testing for compliance with specifications is performed by ProMed's in-house ISO 17025-accredited laboratory or an approved contract lab.

Calculation of Yield

Although many colourants and mix ratios of activators and resins are critical in silicone moulding processes, traditional device manufacturing processes do not require calculation of yield. To comply with the pharma calculation of yield requirements, ProMed implemented comprehensive batch records to calculate and document the theoretical yield and actual yield of drug in components that have a drug constituent. The batch records are predefined through process development and process validation to ensure that the specified loading and elution targets are achieved.

It is important to note that ProMed's combination products typically consist of a moulded silicone or resorbable polymer structure impregnated with the drug substance or API (Figure 3). Once an API is fully encapsulated within a polymer matrix through the moulding processes, the next step is to confirm the drug's elution profile and burst. In other words, to test and confirm how fast the drug substance elutes or discharges from the polymer. This complex analytical testing is performed in-house using validated methods or by an approved contract laboratory, as appropriate. The results are used to confirm actual yield and that the drug elution profile meets specifications. Conforming product is released for final packaging or further processing by quality assurance (QA).

Tamper-Evident Packaging

ProMed does not currently manufacture over-the-counter (OTC) drug products and, as such, tamper evident packaging is not a requirement. However, in its combination products area, it does use non-resealable pouches and labelling practices that comply with and constitute tamper-evident packaging. If breached or missing, a consumer can reasonably be expected to determine that tampering has occurred.

Expiration Dating

Expiration dates for combination products with a drug constituent are established through the product development process while working closely with the pharmaceutical customer. Expiration date testing and ageing studies are established in accordance with the requirements of 21 CFR 211.166 to meet customers' requirements, with the stability programme managed by ProMed, an approved lab or the customer. It is ensured that drug product meets applicable standards of identity, strength, quality and purity at the time of use and each individual unit is labelled for sale with an expiration date as determined by appropriate stability testing.

Testing and Release for Distribution

ProMed samples and tests each batch of drug product for conformance to specifications, including the identity and strength of each active ingredient, prior to release. Samples are collected according test plans defined in approved batch records, which include the method of sampling and the number of units per batch to be tested.

Once the samples are tested, the QA team verifies that the test results conform to predefined acceptance criteria and that the samples and results statistically represent the entire batch prior to approval and release. Any batch failing to meet established standards, specifications or any other relevant quality control criterion are rejected. Due to the nature of manufacturing moulded combination devices, reprocessing is not usually possible.

Special Testing Requirements

ProMed tests each batch of drug product purporting to be sterile and/or pyrogen-free using an approved contract laboratory to verify conformance to such requirements prior to product release. The test procedures are included in the approved batch records.

Although ProMed does not manufacture ophthalmic ointments, the company does manufacture implantable, drug eluting ophthalmic devices. ProMed ensures that these products have predefined requirements regarding the presence of foreign particles and harsh or abrasive substances, and that each

ABOUT THE AUTHORS

Bob Parsons has over 28 years of experience in quality systems, regulatory compliance, programme management and product development within the FDA regulated medical device, pharmaceutical and biotechnology industries. His quality assurance expertise includes certification as a lead auditor, performance of quality system gap assessments, system enhancements, alignment and implementation of all quality elements including design controls, risk management, purchasing controls, change control and post-market surveillance. Regulatory experience includes; ISO 13485, 9001 and 14971 certifications, providing guidance for FDA and CE clearance and a designated management representative as well as company representative and lead interface during FDA and ISO audits. He has extensive experience in 483 and warning letter resolution and working within consent-decree environments.

Dr James Arps has over 20 years of experience managing product development and commercialisation of medical devices, advanced coatings and drug delivery technology. He has worked with both industry and academic partners, guiding products through all stages of development from conceptualisation through to customer release. At ProMed Pharma, he oversees programme development activities for polymer-based drug releasing implants and combination device components. He works with a team of engineers to develop new drug delivery vehicles as well as robust manufacturing processes and platforms for controlled release of drugs from a variety of materials for applications in cardiovascular, women's health, ophthalmology and otolaryngology. He has a PhD in Applied Physics from Vanderbilt University (Nashville, TN, US) and an MS in Management of Technology from the University of Texas at San Antonio (TX, US).

batch of product is tested and confirmed to meet these specifications.

Because many moulded combination devices are formulated for controlled or extended release, drug burst and elution profiles are critical to product performance. To confirm how fast the drug substance elutes or discharges from the silicone matrix, analytical methods for dissolution and quantification are validated and performed in-house or by an approved contract laboratory.

Reserve Samples

ProMed retains an appropriately identified reserve sample from each lot in each shipment of active ingredient or released product. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether it meets established specifications, except for sterility and pyrogen testing. Reserve samples are retained for all drug product samples and excipients for one year after the drug product expiration dates at ProMed Pharma or at the customer's site.

Reserve samples are stored in a product-suitable environment in a closed container. The reserve samples are scheduled through ProMed's PM system for visual examination at least once a year to ensure that the sample integrity is maintained.

Other Requirements

ProMed has a formal procedure for performing annual product quality reviews (APQRs) for each drug product at the end of the first year of a product's commercial manufacturing and every year thereafter. All manufacturing process parameters, failed batches, OOS, non-conformances, complaints or other quality related events are evaluated for trends, systemic issues and opportunities for improvement. As a contract manufacturer, the report is shared with the customer and any changes are evaluated, validated, and approved by the customer prior to implementation.

Drug products in high concentration areas may pose a threat to employee health and safety. ProMed also has a programme for assessing overall personnel health and the protection and safety features required to keep them safe. To prevent exposure, a risk analysis is performed for each API and appropriate containment is specified.

CONCLUSION

In summary, with a dedicated quality system and proper cleanroom facilities and resources, ProMed Pharma has conquered the challenges associated with manufacturing combination products and is able to consistently supply quality drug products to pharmaceutical and device manufacturers. ProMed's expertise and experience in combination products, including drug eluting vaginal rings, glaucoma treatments and diabetes monitoring systems, has added great value to customers, from the planning stages through regulatory submissions and sustainable manufacturing.

ABOUT THE COMPANY

ProMed is an industry-leading supplier of small silicone components for Class III long term implants. Founded in 1989, ProMed has been successful in combining state-of-the-art equipment and tooling to produce tightly toleranced parts for medical devices that are sold in the US, Europe and Asia. ProMed began moulding silicone parts with a pharmaceutical constituent in 2005 and is headquartered in Plymouth (MN, US), with manufacturing facilities in Plymouth, Maple Grove (MN, US) and Puerto Rico.

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INTEGRATING CONNECTED HEALTH IN RESPIRATORY: THE MANUFACTURING CHALLENGE

In this article, David Belton, Director, Quentis, highlights an often undiscussed aspect of the move towards connected drug delivery devices, the impact on manufacturing. Using inhalers as a reference point, he runs through several of the concerns and decisions that will need to be addressed for successful mass production of such devices.

INTRODUCTION

For anyone monitoring current drug delivery trends, it is now clear that connected health devices are the next significant change to drive the industry forward. The impacts to patients, payers and healthcare providers has been thoroughly examined with many of the benefits and disadvantages now well understood by the industry as a whole.

What has received less focus is the potential impact to pharmaceutical manufacturing supply chains. This is a topic worth consideration, as the precedent set over the last decade by the ever-increasing integration of electronics into modern life, alongside the rising expectations of patients as informed consumers, is creating a driving force that will likely lead to increased integration of electronics into pharmaceutical manufacturing as well. This article focuses on disposable, multiple-dose drug delivery systems, comprising of mainly respiratory products, such as metered dose inhalers (MDIs) and nasal sprays, rather than reusable refillable systems where manufacturing of electronics and pharmaceuticals can be kept separate.

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PATIENT EXPECTATIONS

Looking beyond the capabilities and needs of a connected health device, one of the most significant trends we have seen in the computer and smartphone arenas over the last 10–20 years is seamless connectivity. We expect our phones to move invisibly between network coverage and wi-fi and our peripherals to self-install when we plug them in. Extrapolating this trend to connected health, what will a patient expect from a connected medical device?

- Simple, automated connection, for example to a smartphone
- The device to be "self-aware", knowing what product it contains, its strength, number of doses remaining, etc.

Simple connection has been addressed through the use of Bluetooth Low Energy (BTLE) and similar technology. We can see this trend in the development of smart insulin pen-injectors with the development from stand-alone "memory" pens with no connectivity, to docking stations and ultimately to modern self-connecting devices.

The second area, having a "self-aware" product, will become more important as connected health becomes more common, particularly for inhalers. This is because asthma and COPD patients will very often carry multiple inhalers, for the following possible reasons:

- They've been prescribed one or more inhalers for maintenance/reliever purposes
- They keep multiple inhalers of the same product in parallel
- Family members use similar products (and each wishes to track his or her own use on one device).

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While it is well understood from prescribing guidelines that many patients will receive multiple products, the use of the same product in multiple inhalers is also common. For relievers, patients will often hold one at home, one at work and keep one in a bag or pocket. For maintenance therapies, patients will often ensure they get their replacement early, may use them in an *ad hoc* overlap or can also deliberately manage an offset so, for example, they have enough product for a holiday.

In these cases of multiple products and multiple devices, the expectation of connected health is that all of these products will not only be uniquely identifiable, but also clearly identifiable to the patient within an app. This shows how important it is that each inhaler is "self-aware" and capable of indicating key information, such as what type of product it is and how many doses remain, to a phone or other device.

Another probable expectation for increased integration between a drug delivery device and electronics is the ability to deliver additional functionality to patients and healthcare providers, moving beyond recording dose and time to measuring physical use properties, such as orientation, shaking and flow rates, which will likely require additional sensors and therefore deeper integration.

IMPACT ON MANUFACTURING

With a requirement for "self-aware" and easily connected products, this leads to two main conclusions that can be drawn with respect to the supply chain:

- The pharmaceutical and electronic manufacturing processes will become more interconnected.
- There will be a need to program, or otherwise associate, the device with product information within the supply chain.

Interconnected Manufacturing

There are a number of points where the electronic element of a drug delivery system can be brought together with the primary packaging:

- By the patient
- During packaging
- As an add-on process to standard drug delivery system manufacture
- As part of the drug delivery system assembly process
- As part of a pre-made sub-assembly.

> "Early design decisions on electronics will tend to have far more fundamental implications for manufacturing than for standard drug delivery devices."

Considerations that inform when this integration occurs in the supply chain include ease of compliance with electronic disposal standards, such as the waste electrical and electronic equipment (WEEE) directive, and the design needs or restrictions. A crucial point to note is that early design decisions on electronics will tend to have far more fundamental implications for manufacturing than for standard drug delivery devices. The following section looks at some of the fundamental manufacturing impacts of these decisions.

Product Identification

With many patients carrying multiple inhalers, standard pharmaceutical product identification is achieved by adding manufacturing labels at the end of the manufacturing process. These contain product, strength, batch number, expiry and serialisation information, and are usually specific to a particular geographic region. This typically requires a high number of label variants to be held in stock. This works because labels are low cost and holding many variants is not an issue. It often allows primary and secondary product manufacturing to be standardised with only late-stage customisation of labels and packaging.

When looking at connected devices, one option is to have an equal number of electronic variants as there are label variants, containing the same level of information. These would need to be pre-programmed by the electronics manufacturer, held in stock and added to the product at the appropriate time. This poses some challenges:

- **High Cost:** While labels are costed in cents, electronics are costed in dollars and holding a high number of variants may not be cost effective to the supply chain.
- **Shelf Life:** The electronics will be expected to have a shelf life, most likely based on the battery being used. A five-year shelf life sounds comfortable but if there is a three-year on-market requirement and six months is taken up in the external supply chain then the effective time in a pharmaceutical supply chain may effectively be only 18 months. Low-volume, small-market variants could certainly approach this, especially if the electronics supplier has a large minimum order quantity.
- **Unique Data:** Some data will not be pre-programmable, like a finished batch number. If the app allows for elements of production data to be accessed, giving the patient access to this data would allow them to know the expiry date of their product and potentially allow them to confirm that it is not counterfeit.

The natural alternative to this is to build a level of programmability into the device itself. This has different pros and cons:

- **Stockholding:** If the electronics element can be programmed with data at a late stage there may only need to be one variant held in stock. This reduces the cost impact and the risk of having high-value, low-volume products held in stock and also allows simpler management of logistics with a product of limited shelf life.
- **Programming/Data:** Programming will need to occur in final assembly of the device or during packaging operations. Options include contact or non-contact data transfer. Decisions on this would depend on the technology being used. Non-contact via Bluetooth is unlikely to be viable in a manufacturing environment due to the time to synchronise, the need for internal power and ensuring that the intended product is programmed rather than ones adjacent in the line. An RFID option would be relatively straightforward as the chip is powered via external induction and data transfer can be local to the intended device. A third option is for data load via direct contacts. Similar to the RFID option the data can be loaded quickly and the device externally powered but does require electrical contacts to be in a position the equipment can access.

"Consider a low cost pMDI actuator failing an airflow test. As a single moulded item, it is of low value and is scrapped. If the same failure occurs with high value electronics integrated, this failure may now prompt a different response."

Independent of the option for programmability there are other key factors which apply to any device electronics:

Battery Power

In any design the issue of battery power and battery life will be a significant challenge. The three areas to consider are:

- The energy required by the device over the lifetime of the product
- The total energy in the battery
- Energy losses from the battery.

Energy requirements and battery capacity will be core design considerations in product development. In the supply chain, it is generally energy loss that requires management. A fundamental consideration is that energy losses from a battery will be much lower before it is used if it is isolated from the circuit. In terms of manufacturing, having a disconnected battery brings two challenges: first, as previously discussed, any data loading would need to be externally powered (as would testing); second is how to connect the battery for use by the patient. Options include an isolation pull-tab that is to be removed by the patient and, more elegantly, a battery that activates on first use.

Product Quality & Testing

It is a reasonable assumption that the functionality of any electronics will need to be tested during manufacture at the supplier. With any fully integrated device there is a question of whether testing of the electronics' performance also needs to occur once the device and primary pack is complete. This will be very much dependent on its functions. If, for example, it has a primary function such as dose counting or confirming dose delivery, then it can be expected that the same quality expectations as are required of equivalent mechanical systems will apply. Secondary functions, such as patient reminders and tracking of data will need to be considered on a case by-case basis as to whether late-stage testing is required.

If testing is deemed necessary, options include full physical testing by operating the device and checking if the expected output occurred, simulating use with representative input signals and confirming outputs, or by testing specific sub-systems. Much like the decision on when to program the unit with product date, these requirements need to be considered early in the development process as they will affect both how the electronics are designed and how the device is assembled.

Skills and Capabilities

With the introduction of electronics into a pharmaceutical supply chain, new skills and capabilities will be required. While some may be obvious, with engineering teams requiring electronic and software manufacturing/test knowledge, the majority of supply chain functions will also be impacted. For example, production and logistics areas may need to understand special handling and storage requirements, such as electrostatic prevention. Quality groups will be expected to understand electronic products and to support testing, investigations and audits of suppliers. Similar expectations also apply to procurement and external technical supply-chain groups to ensure electronics suppliers are meeting appropriate standards.

Cost

It is clear that the addition of high-value electronics will increase product unit costs. In manufacturing the impact of where high-value items are introduced into the supply chain also needs to be carefully considered, particularly around the cost of waste. This is best demonstrated using an example.

Consider a low cost pMDI actuator failing an airflow test. As a single moulded item, it is of low value and is scrapped. If the same failure occurs with high value electronics integrated, this failure may now prompt a different response. This could be a retest, recovery and reuse of the electronics or, if still scrapped, segregation for recycling purposes.

This type of reconsideration will not only affect cost impact assessments after integration, but may also drive enhanced testing or testing of components earlier in manufacturing to ensure they pass before integration.

"In manufacturing the impact of where high-value items are introduced into the supply chain also needs to be carefully considered, particularly around the cost of waste."

CONCLUSION

With patient expectations on ease of use for smart devices increasing, the lessons learnt from other business areas, such as refillable insulin pens, will need to be adapted to respiratory products. A drive towards integrating self-connecting, "self-aware" devices will move electronics into the pharmaceutical manufacturing supply chain. With deeper integration, a range of new challenges will be seen, including programmability, testing and both component and cost management.

Nearly all of these factors will be constrained based on the product requirements and the design choices made. To guide these concepts towards a product capable of effective industrialisation, early application of Design for Manufacture (DfM) and understanding of manufacturing impacts right from the point of concept will become ever more important in the development process.

ABOUT THE AUTHOR

David Belton is Founder and Director of Quentis, a medical device engineering consultancy specialising in providing design assurance and industrialisation know-how throughout the product lifecycle. Mr Belton has a degree in mechanical engineering from Loughborough University (Loughborough, UK) and has spent 20 years in both the electronics and drug delivery industries, bringing new products to market ranging right from the world's first 3G phone network to world-class dry powder inhalers.

5 THINGS TO CONSIDER
WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize

While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

1. **Development strategy and design consideration**
2. **Situation analysis and patient compliance**
3. **Connectivity ecosystem**
4. **Wireless subsystem**
5. **Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.

A "KODAK" MOMENT FOR THE PHARMA INDUSTRY?

In this article, Pari Datta, PhD, Senior Innovation and Research Consultant, and Nick Rollings, CEng, MIMechE, Consultant Medical Device Engineer, both of Cambridge Design Partnership, discuss the concept of personalised medicine, with particular reference to oncology, and how it represents both an opportunity, for those who can solve its manufacturing conundrums, and a threat, for those who find themselves unable to adapt to a changing therapeutic paradigm.

The pharmaceutical industry we know today began with the synthesis of early, simple medicines. Pharma companies such as Merck and Bayer originate from individual pharmacies, the dye industry and fine chemical companies that started to bulk manufacture antiseptics and painkillers. The second industrial revolution made mass production of medicines possible – a development that has lasted to the present day, with antibiotics still manufactured in batches of hundreds of thousands to treat vast numbers of patients.

As the pharma companies grew, they moved away from broad portfolios of consumer products to the first mass-market pharmaceuticals such as insulin and penicillin. Several decades later, the idea of the blockbuster drug became key to many pharma companies – they began to look for drugs that could make US$1 billion per year, such as Tagamet (cimetidine) and Prozac (fluoxetine).

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ONE SIZE FITS ALL

As a blockbuster, Prozac was a wonder drug that could treat millions of people. It was taken by 40 million people across 100 countries at its peak, adopting a "one size fits all" approach that was the mainstay of the pharma industry for decades. Despite this approach being used for decades, increasing insight in the genomic era since 2000 identified that certain therapies will only work for certain sub-populations of patients, depending on the presence of specific genes in a patient's genome.

The "one size fits all" model has been a particularly thorny issue in oncology. Small-molecule chemotherapy drugs, such as platins and taxanes, are only effective on some cancers and specific patients, whilst causing extensive side effects. The term "personalised medicine" has arisen over the past 20 years – because one size does not, in fact, fit all, especially for cancer therapies. The classic example of this has been the monoclonal antibody Herceptin® (trastuzumab), which is only given to patients whose tumour over-expresses the HER2 gene.

There has been a boom in gene targets that can be used for drug selection in the same way, empowered by our greater understanding of the human genome. Resulting companion diagnostic tests now enable clinicians to prescribe the correct drug first rather than taking an empirical approach.

STRATIFIED MEDICINE

"Stratified medicine" is a term that has been used for the last decade. Whilst not truly "personalised" for individuals, the latest generation of cancer therapies is now heading towards treating specific individuals in an 'n=1' scenario rather than groups of people in the traditional 'n=millions'."

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approach identifies a specific but smaller sub-population of patients that can be treated by specific therapies. With Herceptin for instance, in the 20-30% of breast cancer cases that are HER2 positive, the benefit is that the therapy will be particularly effective against their specific form of cancer. Such biologic-based therapies with high specificity work for highly specific patient groups whilst still enabling blockbuster-type revenues. However, manufacturing challenges associated with biologics mean that they still need to be manufactured in relatively large volumes to make the economic unit costs acceptable.

TOWARD PERSONALISED MEDICINE

The latest generation of cancer therapies is now heading towards treating specific individuals in an "n=1" scenario rather than groups of people in the traditional "n=millions". Advanced therapies (ATs), such as cellular therapies, are being developed for multiple conditions, from neurological to ophthalmological, with nearly 50% of therapies in the pipeline for cancer treatments based on immune and blood cells.

Some cellular therapies are allogenic therapies, where immune cells are taken from one donor, manipulated and then administered to many patients. In some ways, these therapies can be treated like traditional biologics – scaled up using fairly standardised methods and cryopreserved until they are required. There are some challenges with preserving these over a long shelf life, but the model is still relatively scalable, and therefore pharma originally favoured this approach based on traditional biologics. Specific challenges remain, however – scale up, for example, is still not as straightforward as merely increasing the bioreactor volume, as cell lines can exhibit differing behaviour at larger volumes. As another example, there are challenges in controlling agitation rates in larger fermenters, which can damage cells – yet cell function and quality is crucial to preserve product efficacy.

A second category of therapies is autologous cell therapies. These therapies require harvesting of cells from each patient, processing them and then returning them to the patient with modifications – making the body more capable of fighting a particular disease or condition. Recently approved chimeric antigen receptor T-cell therapies, such as Kymriah® (tisagenlecleucel, Novartis), involve modifying T-lymphocytes (T-cells) from a patient to provide them with the ability to detect malignant B-cells within blood-based cancers. The modification involves the use of viral vectors to alter the genome of the T-cells to express an altered receptor (chimeric) to target CD19 proteins, which are expressed in malignant B-cells in blood-based cancer. The key advantage of autologous therapies over allogenic therapies is there will be no immunologic reaction, as the cells are sourced from the patient. Despite the manufacturing challenges, autologous therapies have become popular, with multiple candidates in development.

Autologous therapies form the majority of cellular therapies undergoing clinical trials. Kymriah® was approved last year to treat B-cell acute lymphoblastic leukaemia in young people whose cancer has either recurred or always been resistant to other therapies.

RESULTING CHALLENGES

With the emergence of autologous ATs, pharma companies are less acting as a mass manufacturer of medicines, but rather as a solution provider enabling the modification of cells. The resulting challenge here is scale-out rather than scale-up, whereby one manufacturing batch treats one patient and not whole populations. Cells must be initially harvested from each patient individually. The harvested cells require careful handling as they are patient specific and cannot be replaced during processing. The cells must then be transported to a cGMP-compliant facility, without suffering damage or disruption during transportation. At this location, the cells are modified within aseptic processes by highly skilled scientists. The cells are then stored before being transported back to the patient's bedside within the hospital, where they are infused back into the patient. Transport is vital to both harvesting and re-administration to the patient, so conditions must always be monitored and samples tracked. Sterility and traceability to the original patient is key at all stages of the process.

It is therefore no surprise that manufacturing autologous therapies is expensive. Kymriah® has been priced at $500,000 per patient, which is a large cost despite the resulting value – completely curing a patient's cancer – being clear. It is easy to see where the costs come from, the patient needs to be kept in hospital for long periods and cells need to be removed and

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manipulated with agents – such as viruses – which, in turn, have been specifically manufactured to activate them. This process is then carried out manually by a highly skilled team. Every step in the 22-day process requires monitoring and quality checks to ensure a high-quality product.

Manufacturing must be carried out in aseptic locations, using many manual steps that can only currently be executed by trained personnel and that carry a high risk of errors. Many of the errors in traditional pharma processes are due to human error, and in the case of cellular therapies, such errors can lead to non-functioning therapies and life-threatening results for the patient. Cells are much more sensitive to damage than traditional biologics, which in turn are much less robust than small-molecules. The cost of failed batches contributes to the high costs of cellular therapies.

This means that ensuring quality throughout each precisely controlled manufacturing step is vital. The high cost of cellular therapies means they can't be available to all who need them. It also becomes too challenging to sustain a high enough gross margin for commercial viability of the products.

POTENTIAL SOLUTIONS

Following regulatory clearance in 2017, attention is now turning to resolving these manufacturing challenges for ATs. There are many classes of solution which become immediately applicable to tackle the issues. Closed systems – separating operator from product – are one such solution, enabling the high costs associated with high-grade GMP and clean locations to be avoided. Closed systems allow production to remain aseptic and the overall classification of a manufacturing location to be downgraded. They also reduce the risk of contamination by operators and enable therapies for multiple patients to be manufactured simultaneously within the

same manufacturing facility. Single-use, disposable technologies also contribute to reducing the risks of contamination.

Automation will become key to reducing production costs, improving both standardisation and quality. By implementing automation, simple manual steps, such as shaking, opening vessels and counting cells, can be avoided. In the example of counting cells, operators must still use haemocytometers to count cells in grids to assess yields, making judgements which can still seem quite subjective. Automation will reduce the skill level required by operators, enabling manufacturing processes to be carried out in multiple locations whilst, crucially, maintaining product quality.

Automation will also enable the collection of significant data sets during the production process, which will in turn enable continual improvement and refinement of the production process, maintaining quality and reducing costs. The ability to characterise products during manufacture could be invaluable, e.g. enabling understanding of the nutrient consumption of cells, their metabolite production and concentration to monitor overall process quality. Data is generated throughout all steps of the process, including analytics and batch records.

However, there are still questions around what technologies can be used to collect data, how much data is necessary and how best to use it to improve the manufacturing process. Currently, process analytics are performed off-line at set points. There is considerable potential for greater use of in-line analytics for continuous monitoring. There is currently a lack of general monitoring technologies when cell numbers are being expanded. Together with developments in sensing and monitoring technologies, data processing techniques – ranging from classical signal processing to artificial intelligence approaches – could be used to turn measured data into insights and actionable information, such as giving a prediction of cell potency.

More fundamental challenges exist around process steps related to cell modification and cryopreservation. Cell modification is currently carried out using live viral vectors, which themselves are very delicate and need to be handled carefully. Viral vectors can become integrated in random locations within the cellular genome, which impacts robustness in manufacturing. Next-generation gene editing tools, such as CRISPR-Cas9, could solve this problem with more site-specific additions of genetic constructs. Cryopreservation is another key step, performed at the back end of the manufacturing process, increasing the shelf life of products and therefore geographic reach. However, if not managed, inadequate storage conditions could lead to a decline in cell viability and therefore reduced therapeutic effect.

THE NEED TO INNOVATE

At first sight, the quantity and degree of the challenges in manufacturing cellular therapies may seem intimidating. It is, however, worth reflecting on the bigger picture and the enormous potential ATs have to treat patients and cure diseases. In original clinical studies for Kymriah®, the overall response rate in the short term – based on a single infusion of Kymriah® – was above 80% for evaluated patients whose leukaemia could not be cured by any other means. Current manufacturing challenges and high costs could prevent such treatments being used widely, consequently there are considerable opportunities for companies that can solve these significant challenges through innovation and technology. Innovation methodologies such as user-experience mapping, jobs-to-be-done, technology mapping, TRIZ and intellectual property landscaping have proved useful in other applications and could help to elucidate the challenges and discover solutions.

The flip side is that we could be heading for a "Kodak" scenario for companies that remain wedded to legacy processes and miss the opportunity to innovate and embrace a new future. Currently, these challenges are yet to be fully understood and further clarity around the challenges will be required. Whilst this may seem daunting, this scenario actually provides an opportunity for innovative thinking that will enable the entry of new players into the market, with solutions and technologies from other industries. We are already seeing this happen with the intense investment by major Asian companies such as Samsung and Hitachi. These companies can bring insight and fresh perspectives, not wedded to traditional ways of therapy manufacturing.

There are many parallels between the emerging era of ATs and the Kodak story. New entrants eventually took over the photography market as it transitioned from film to digital. Digital photography disrupted Kodak's film-based business model to the point of its bankruptcy, despite once owning 50% of the global photography business and employing 60,000 people. The brutal irony is that Kodak invented the very technology which destroyed its business, through its invention of the original digital camera in 1975. It did not spot or react to the disruptive forces in its industry. It tried to prolong the life of film by creating products which acted as printer docks for its cameras.

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A similar scenario is playing out right now in the automotive industry as new entrant Tesla has popularised the electric vehicle and left incumbents with businesses based on legacy internal combustion engines racing to develop their own electric models.

In a similar way, sticking to the old way of thinking centred on blockbuster drugs could lead to a Kodak moment for even today's biggest pharma companies. It is now possible to envisage manufacturing of cellular therapies reaching the patient's bedside with automated, scaled-out manufacturing approaches and no centralised manufacturing facility required. Companies that innovate, solve challenges and think disruptively could avoid falling into the Kodak trap – and unlock the huge potential enabled by ATs.

ABOUT THE COMPANY

Cambridge Design Partnership is a technology and product design partner focused on helping clients grow their businesses. Some of the world's largest companies trust CDP to develop their most important innovations. Located in both Cambridge (UK) and Palo Alto (CA, US), CDP specialises in the consumer products,

healthcare, energy and industrial equipment markets. Its multidisciplinary staff have the expert knowledge to identify opportunities and tackle the challenges its clients face.

ABOUT THE AUTHORS

Pari Datta, PhD, is an innovation professional who specialises in identifying, building and validating new opportunities for major global companies and emerging start-ups. He has 10 years' experience in leading innovation and strategy programmes, including insight generation, opportunity discovery, commercial assessment, strategy development, concept generation, technology scouting, IP landscaping and the process of innovation. He has led projects in many industries including fast-moving consumer goods, drug delivery, surgical and critical care – specialising in life sciences and diagnostics. He has accumulated extensive technical and commercial knowledge through R&D/commercialisation of early-stage technologies and working as an innovation project manager for a global leader in diagnostics. Dr Datta holds a degree in Biochemistry and a PhD in Genetics.

Nick Rollings, CEng, MIMechE, is experienced in all aspects of multidisciplinary technology and medical device development. He has instigated and led technology creation and development projects in the diagnostics and life science instrumentation sectors and has co-authored papers on various different technologies. Mr Rollings' experience includes multiple biotechnology instrumentation developments. He was also a founding member of a spin off company from a large FTSE 100 technology firm developing a novel diagnostics technology for veterinary and clinical point-of-care applications. Mr Rollings is a chartered engineer and spent time earlier in his 20-year career as a manufacturing engineer, implementing new and modified designs into mass production.

ON drugDELIVERY

2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Sep 2018	Wearable Injectors	PASSED
Oct 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
Nov 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
Dec 2018	Connecting Drug Delivery	Nov 1st 2018
Jan 2019	Ophthalmic Drug Delivery	Dec 6th 2018
Feb 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019
Mar 2019	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 7th 2019
Apr 2019	Pulmonary & Nasal Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery	Apr 4th 2019
Jun 2019	Connecting Drug Delivery	May 2nd 2019
Jul 2019	Novel Oral Delivery Systems	Jun 6th 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4th 2019
Sep 2019	Wearable Injectors	Aug 1st 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5th 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3rd 2019
Dec 2019	Connecting Drug Delivery	Nov 7th 2019

GO WITH THE FLOW – SOLVING POWDER FLOW CHALLENGES BEFORE PRODUCTION

In this article, Jonathan Gaik, Director, Natoli Scientific, discusses the various problems in tablet compression that can be caused by not giving due care to powder flow in the development stage and how, by doing so, what would be serious problems at the industrial scale can be solved in advance.

Ideally, an API powder will be one that flows well, is stable, self-lubricates, compacts well and is not strain-rate sensitive. While all the listed properties are important, the one that is truly critical is powder flow; most challenges in the tableting process begin with, or can be traced back to, flow. In the formulation development process, excipients such as glidants, binders and lubricants are added to the API to improve its flowability.

Challenges originating in the flowability of powders become more apparent when scaling up to full production. A seemingly minor product fault during R&D can become an unmanageable nightmare when scaled up to industrial production, by which point making changes to a formulation is costly and time-consuming. Conducting studies on a formulation during R&D and scale-up can help identify and solve potential powder-flow issues before moving into commercial production.

"A seemingly minor product fault during R&D can become an unmanageable nightmare when scaled up to industrial production, by which point making changes to a formulation is costly and time-consuming."

STORAGE CONDITIONS

Humidity levels within storage or production areas can affect a powder's properties and thus how it flows. Additional moisture can increase a powder's potential to form hydrogen bonds that may cause a more cohesive powder that will restrict flow. Hold-time studies during R&D – establishing the time limits of holding a formulation at different stages of production – are crucial to determining the effects of storage conditions on the formulation. Maintaining an environmentally controlled storage and production area is vital to a formulation's flow characteristics.

BLENDING

Flow difficulties at the blending step often manifest as slow/no discharge or ratholing. The most common causes of these issues are:

- Improper storage
- Poorly selected binder that is too cohesive with the API
- Lack of glidant
- Improper order of addition
- Incorrect blending procedure.

The best way to establish flowability is to compare flow on a Flodex™ powder flow tester (Teledyne Hanson Research, CA, US) with the tablet configuration to determine whether the powder's intrinsic flow is close or equivalent to the cross-section of the tablet press die. For example, testing on a Flodex™ may show that a neat API powder has flowability of 26 mm, with a round tablet design of 12 mm in diameter. In such a case, the formulator would

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need to re-examine the concentration and types of glidants and binders to achieve a target intrinsic flowability of 12 mm or less. Once that has been achieved, lubricants can be added and evaluated for flow.

Material interactions will guide the order of excipient addition and blending procedures. For example, if a glidant is needed, consider a pre-blend step to maximise the interaction between the glidant and the poorly flowing materials. A pre-blend step usually lasts between two to eight minutes. The optimum length of time can be determined using a Flodex™. Blend uniformity (BU) studies ensure APIs are adequately blended with excipients. BU studies can give formulators clear evidence of whether or not a formulation is within specification before moving to the next step in the process.

HOPPER DESIGN AND POWDER SEGREGATION

After blending, the powder is discharged to the hopper, where the formulator must ensure the powder's flow properties are adequate for it to successfully enter the gravity or force feeder. Difficulties when discharging a powder blend, including erratic flow, no flow and segregation, can be due to improper hopper design. Studies are conducted in R&D to calculate measurements like angle of repose and wall friction based on the powder properties. This information can be used to design the hopper's shape and determine the best material of construction and surface finish for encouraging powder flow.

Powder segregation within the hopper may result from formulation design or improper transfer. One type of segregation, called sifting, occurs when gravity or tablet press vibrations cause larger particles to separate from the smaller particles. Smaller particles filter to the bottom while the larger particles rise to the top (Figure 1). Particle size distribution and density of all materials within the powder blend are key considerations to prevent sifting segregation. Researchers can conduct studies according to ASTM International standards to help understand whether segregation is occurring and by what mechanism.

Segregation happening at this point in the process can affect tablet quality, possibly causing capping, lamination and/or high ejection forces. Conducting content uniformity (CU) studies can help determine

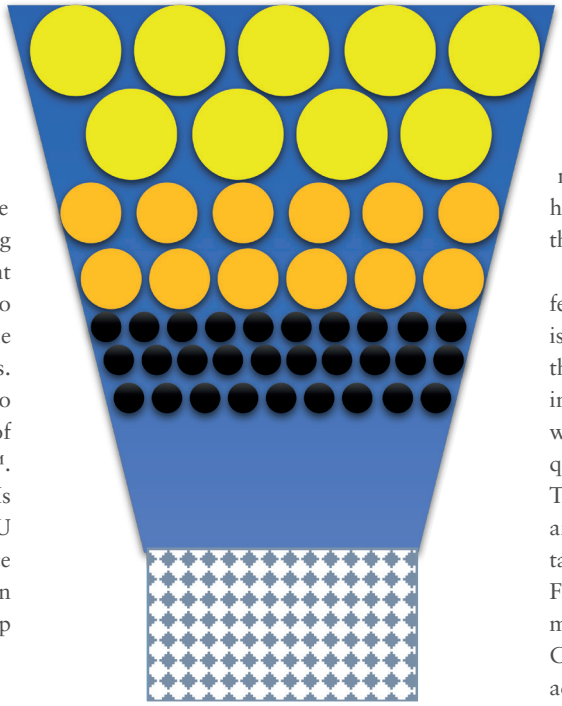

Figure 1: Particle size and density variation within a hopper under sifting.

whether the batch is consistent and within specification. CU studies should follow the guidelines set forth by the US FDA under 21 CFR 211.110.

TABLET PRESS CONSIDERATIONS

Flow challenges on the tablet press can cause tablet quality issues such as weight variability, content uniformity and/or tablet defects.

Weight variability can be driven by a poorly flowing powder or agglomeration by a material within the powder. Each die in the tablet press sits under the opening in the feed frame for only a small amount of time, usually milliseconds. Therefore, the flow rate must be calculated and tested to ensure that the powder flow can keep pace with the feeder and turret speed, thus adequately filling the dies to the correct weight. Agglomeration might not be detected in flowability studies, however it can become a localised flow event that randomly causes weight variability.

Additionally, matching the turret and feeder speed to the flow rate of the powder is necessary to prevent over-blending in the feed frame. Over-blending can result in segregation or excessive lubrication, which can, in turn, lead to poor tablet quality in terms of CU or compactibility. To identify these issues, CU samples are typically collected in set intervals as tablets are produced on the tablet press. Figure 2 shows an example CU assay at 15 minute intervals during tablet production. CU1 shows tablets that are within the acceptable content uniformity range, CU2 shows an example of sifting segregation and CU3 shows irregular, non-uniform tablet content due to over-blending. CU samples can help identify specific problems based on the results, however, unless they are paired with BU studies, they

> "Powder rheology studies, such as shear strength and wall friction, alongside flowability, can be performed throughout the R&D process to help demonstrate a powder's flow characteristics."

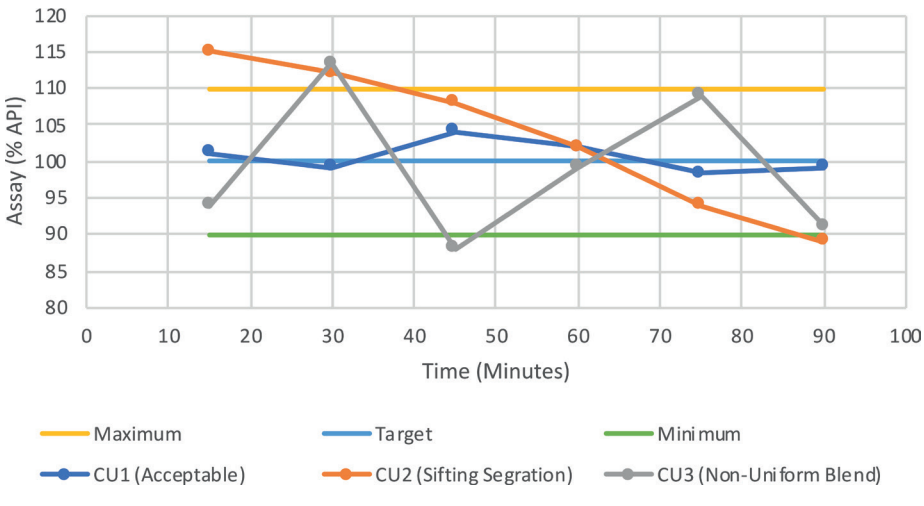

Figure 2: Tablet content uniformity assay studies.

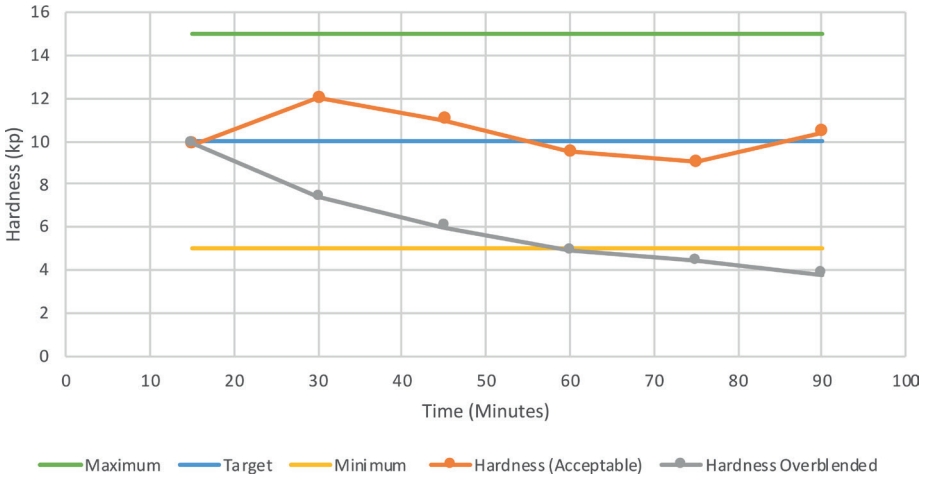

Figure 3: Tablet content uniformity hardness studies.

will not be able to isolate where the issue is occurring. Changes in hardness can be identified with the same CU studies. See Figure 3 for CU tablet hardness study.

Finally, poor powder flow can result in tablet defects, such as sticking and picking, which may be caused by entrapped air within the tablet press die. Formulation design, engraving, tooling material or coating can improve powder flow during the compression cycle and thus reduce tablet defects. Gentle curvature in engraving cuts results in more laminar and less turbulent powder flow. Tooling material and metal coatings should be selected to decrease the coefficient of friction while increasing release characteristics, which will also improve powder flow.

ENSURING GOOD POWDER FLOW

A poorly flowing powder can affect tablet quality at every step in the process. Key factors to consider when encountering a powder that doesn't flow well are:

- Formulation design
- Storage conditions
- Tablet design
- Mechanical design of processing equipment.

Powder rheology studies, such as shear strength and wall friction, which can be conducted on an FT4 Powder Rheometer® (Freeman Technology, UK), alongside flowability studies on a Flodex™, can be performed throughout the R&D process to help demonstrate a powder's flow characteristics. A thorough process development, including conducting BU and CU studies and determining turret and feeder speed, also helps optimise production and reduce time involved in troubleshooting.

Minor powder flow issues during R&D can turn into major headaches once scale-up to industrial production begins. Conducting studies throughout R&D and scale-up can help identify and isolate where in the process a formulation issue began. Powder flow also can vary from lot to lot, which needs to be understood during R&D. Most problems that manifest on the tablet press start with the powder and its flow properties, so it's important to understand how a powder will perform under every circumstance.

ABOUT THE COMPANY

Natoli Engineering Company is a world-leading company in tablet-press tooling manufacturing. Founded on the principle of manufacturing and delivering the highest quality products at a fair price with exceptional customer service, Natoli continues to build on 40 years of innovation and industry leadership.

ABOUT THE AUTHOR

Jonathan Gaik received his BS in Chemistry from the Missouri University of Science and Technology (Rolla, MO, US). He has worked in solid oral dosage formulation and process development in the pharmaceutical and food industries. Mr Gaik has various patent applications for his work combating the opioid crisis via abuse-deterrent dosage forms. His current interest is driving the development of continuous manufacturing and identifying first principles sources of solid oral dosage formulation-related issues during processing. Mr Gaik is currently director of Natoli Scientific and co-director of the Natoli Institute for Industrial Pharmacy Research and Development at the Arnold and Marie Schwartz School of Pharmacy at Long Island University (NY, US).

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INDUSTRIALISING DRUG DELIVERY SYSTEMS – A RISK-BASED APPROACH

Here, Catherine Thacker, Director of Pre-Automation Solutions, and Tom Hayes, Vice-President of Global Sales, Life Sciences, both of ATS Automation, discuss the company's methodology for developing a manufacturing strategy for a drug delivery device, from fresh design to mass-produced product.

PLANNING FOR PRODUCTION

The successful industrialisation of a drug delivery system is defined as the ability to assure the supply of a quality product in a sustainable way. Let's consider the launch of a new drug/delivery device combination – we will call it OUCHLS for lack of a more creative name. R&D has a great product design, early users and clinical trials are returning favourable results, regulatory affairs is not anticipating any roadblocks with the submission, and marketing is confident in market interest. The operations team turns its attention to preparing for commercial supply.

At ATS Automation, our experience has been that most discussions start with, "How much should I budget for the purchase of production equipment?" and, "Who can I buy equipment from to manufacture OUCHLS?" These are useful questions, but the first questions should be, "How will I manufacture OUCHLS so it meets the desired total product cost?", "Is automation an option?", and "If not, what other manufacturing options are available to me?".

Although primarily known as a bespoke automation solutions provider, ATS also works with customers to plan commercialisation projects and to provide post automation services. As Figure 1 shows, ATS has expertise and capabilities well beyond those of solely a machine designer and builder. This unique service offering provides a continuity and accountability that is essential in mitigating project risk and ensuring a smooth execution.

> "The definition of success for any industrialisation project bears repeating: the assured supply of a quality product and demonstrated sustainable performance."

SO WHERE DO WE START?

The definition of success for any industrialisation project bears repeating: the assured supply of a quality product and demonstrated sustainable performance. The implications are that:

- The market potential is understood, including end-user interest and tolerated pricing.
- The product, process and assembly equipment requirements are defined.
- A business analysis identifying anticipated product costs and overall cost of ownership is complete and comprehensive, supporting some level of investment.
- The technologies and processes used during development can be scaled or transferred to larger volumes and higher throughputs.

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/ GMP review & validation planning	/ Qualification	/ Spare parts
	/ Repetitive equipment manufacturing	/ Modifications, upgrades & relocations
	/ Data acquisition & MES	

Figure 1: From planning to post-installation services, ATS complements the customer's team throughout the project lifecycle.

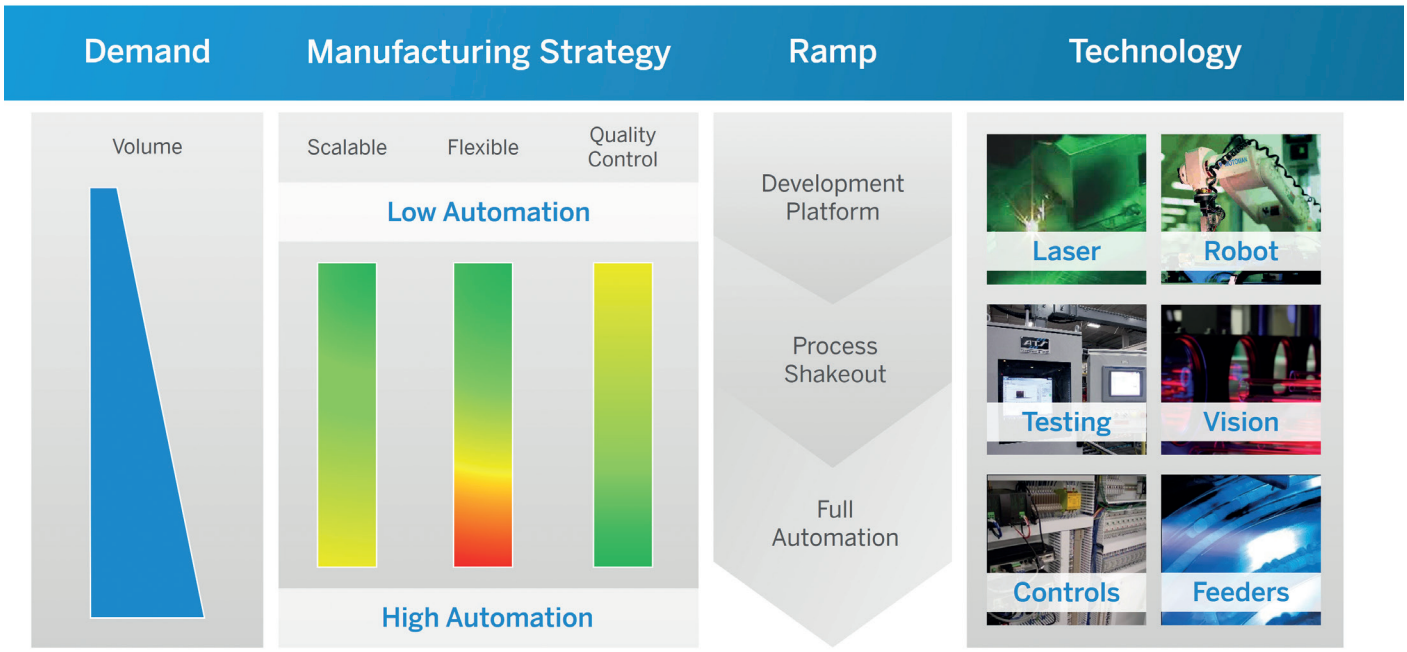


Figure 2: Developing a manufacturing strategy starts with understanding the customer's requirements.

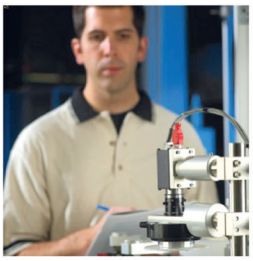
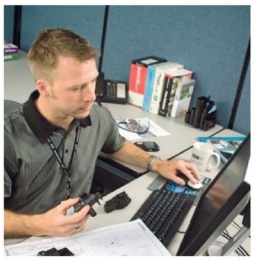
Let's revisit our fictitious product, OUCHLS. Before we can start to identify possible manufacturing strategies, we need to have some level of confidence in the following: the anticipated volume growth over some time horizon, the suitability of the product design for commercial manufacturing, and the soundness and robustness of the manufacturing process (Figure 2).

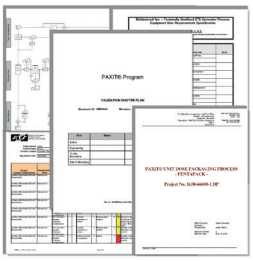
The successful assembly of OUCHLS in a lab environment does not guarantee a similar success in mass production. ATS' "Pre-Automation Solutions" discipline is focused on assisting customers to establish their requirements, develop confidence in their product-specific knowledge and to arrive at a deliberated manufacturing plan and justified financial investment strategy.

A PHASED APPROACH TO ARRIVING AT A MANUFACTURING STRATEGY

To assist customers with product launch programmes, ATS proposes pre-automation services. This offering can help in the deliberated evolution from small-scale product assembly, typical of clinical trials, to the large-scale product assembly associated with commercialisation. Our process helps mitigate some of the larger scale-up concerns, such as:

- How do we assure the quality of the product is consistent?
- Will the product supply chain and manufacturing process be robust?
- Will the process have long-term sustainability?



Mobilize **Explore** **Optimize** **Recommend**

- / Site visit
- / Process mapping
- / Stakeholder interviews
- / Risk assessment
- / Benchmarking
- / DFM/DFA
- / Concept development and analysis
- / Block planning
- / New technology & approach research
- / Financial analysis (ex. TCO)
- / Layouts
- / Simulation
- / Animation
- / Technical specifications
- / Reports &/or business plan
- / Proposals
- / Implementation planning

Figure 3: A disciplined approach to formulating a manufacturing strategy can eliminate waste during implementation.

Over the past 15 years, ATS has developed a methodology for developing appropriate manufacturing strategies that has been successfully deployed with many medical device and combination product customers (Figure 3). Our disciplined approach of "Mobilising, Exploring, Optimising and Recommending" has helped manufacturers identify risks early so that they can be mitigated before significant resources have been invested.

Working collaboratively with the customer, ATS builds a team of GMP-compliant manufacturing and automation experts to compliment the customer's subject matter expertise. Together we explore the project and work through the phased approach. Depending on the level of advancement of the project and the availability of the customer's resources, not all activities in Figure 3 may be necessary but, for the purposes of demonstration, let's assume that OUCHLS needs to go through the entire process.

Mobilise

Before we start to anticipate equipment possibilities, we need to document what we know about OUCHLS and the industrialisation project. This may sound trite, but gaps in information, false assumptions and mismatched expectations can quickly derail a project. This is a good time to bring someone onto the project who does not have intimate knowledge of OUCHLS. This individual, or group of individuals, will not be constrained by foreknowledge and will be quite happy to ask, "But why?" in order to uncover what is known and not known, and where there is alignment and divergence. By interviewing a variety of stakeholders, we will get a very clear picture of the project's current state and what its desired future looks like.

The critical deliverable from this phase is a preliminary user requirements specification (URS) that captures the essence of the industrialisation solution including:

- Product definition, including dimensions, tolerances, functionality, etc.
- Process flow maps or value stream maps, including cycle times, parameters, ranges, tolerances, criticality, risk assessments, etc.
- Definition of quality, usually articulated through quality attributes and pass/fail criteria.
- Commercial goals or success factors including throughput, flexibility, utilisation, performance, staffing, shifts, facilities, utilities, finance, etc.

Gaps in knowledge and conflicting requirements will be flagged and risks identified for exploration and mitigation in the next phase.

Explore

We have now documented everything there is to know, at least at this stage, about OUCHLS. What comes next?

Figure 4: ATS' vision group demonstrates the ability to identify cannula bevel, defects, orientation, etc.

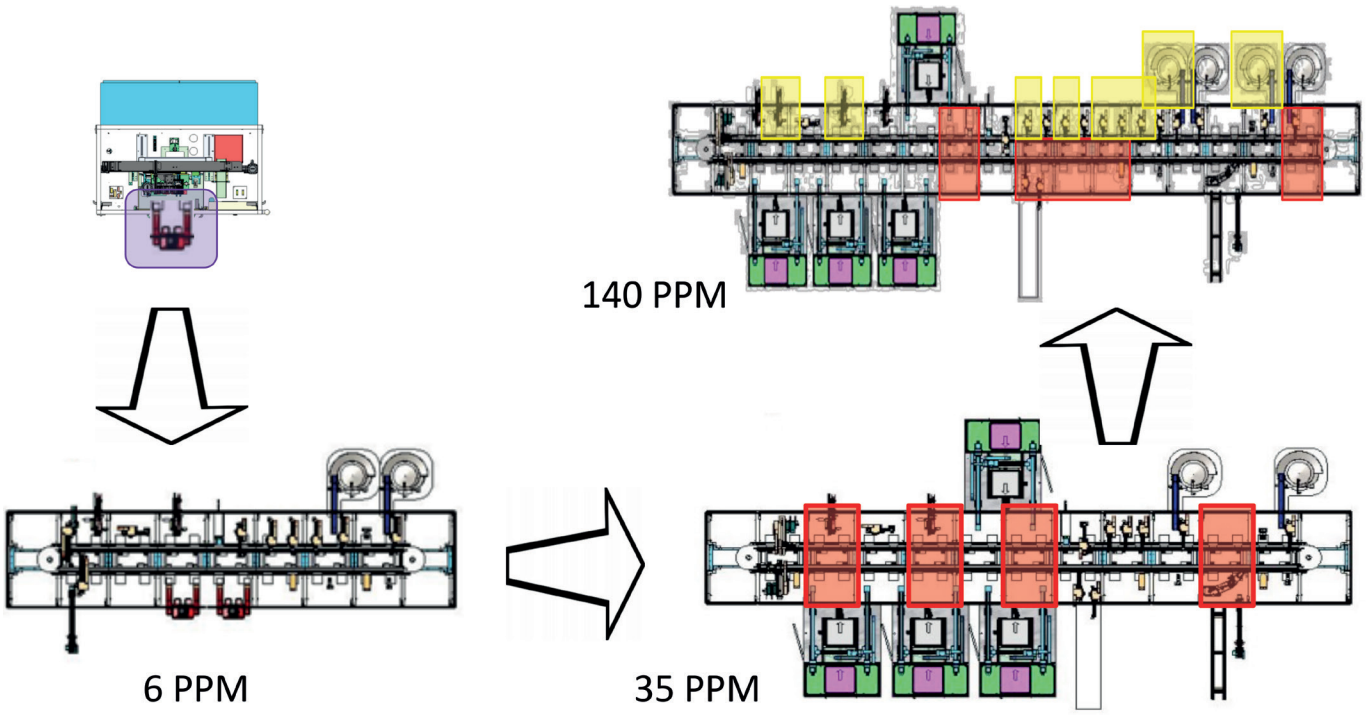


Figure 5: Concepts to consider include those that grow as demand for your product grows.

"As much fun as solving the manufacturing problem is, the trick is to reduce the number of options to a likely two or three."

A natural next step is to take a deeper dive into the product design. Can OUCHLS, in its current iteration, be assembled in a cost effective manner? The input and advice of automation partners like ATS are critical at this stage. They will review how the parts can be fed, handled, oriented and assembled reliably. They will offer suggestions about design improvements that will not detract from the product design intent but will enhance the manufacturability. They will also challenge you on process steps, the order in which they occur and their necessity, and those steps that have significantly different processing times that may influence automation decisions about asynchronous versus synchronous solutions, or parallel path versus linear solutions.

This is also the phase during which we focus on resolving the gaps and risks that we identified during the mobilise phase. It may be necessary to execute engineering studies to fill in process-parameter gaps or to prove out the scalability of a technology or process step. Inspections for specific quality attributes or defects are also study candidates in order to establish robustness and reliability. It can be challenging to characterise a defect in a quantifiable way. For example, OUCHLS may have a lubrication process, but how do we describe an acceptable lubricant dispersal pattern? It can also be difficult to see a defect with machine vision. ATS has a dedicated vision group that regularly executes experiments to demonstrate product and project-specific detection capability (Figure 4).

Any new information arising from the product design review and experiments will be added to the URS so that, as we turn our attention to manufacturing options, we have the most up-to-date requirements. It is at this stage that we can start to identify concepts for the manufacture of OUCHLS that comply with the URS. Concepts to consider include:

- Operational models, i.e. in-house or outsourced
- Automation content, i.e. manual or fully automated
- Throughput or scale, i.e. low or high cycle times or volumes
- Geography, i.e. on-shore or off-shore
- Connectedness, i.e. stand-alone or integrated.

There are also hybrid concepts or those that are variations of those identified. The development of a concept or idea need only be to the point where there is sufficient detail that we can assess the pros and cons in an unbiased way. It does not have to be detailed machine models.

Figure 5 illustrates two points: the level of detail related to describing a concept, and how a concept can satisfy several of the concept considerations. The concept shown is one that ATS developed and implemented for a customer that grew from a small-scale system to support R&D, to a clinical trial supply system, to a fully integrated system for full-scale commercial production. For a product like OUCHLS, this would be an ideal way of gaining experience with automated manufacturing while exercising fiscal prudence until full-scale volumes are required.

Figure 5 makes it is easy to understand how a lean cell with manual operator engagement might be integrated into a material handling platform like ATS SuperTrak®, where some processes are performed by automation. As demand for OUCHLS grows, the SuperTrak® platform can be pulled apart and additional automation integrated to remove dependence on operators and increase throughput. And finally, replicated automation can be integrated into vacant spaces on the SuperTrak® platform to achieve that final increase in capacity.

As much fun as solving the manufacturing problem is, the trick is to reduce the number of options to a likely two or three. The best resource for this is the URS. We can use it at this juncture to evaluate our concepts on their ability to deliver success. In our OUCHLS

OUCHLS Launch - Manufacturing Concepts - Qualitative Analysis Pugh Matrix								
		Capital Investment	Labour Utilisation	Product Quality Risk	Traceability	Capacity	Floor Space	Score
	Weighting	3	5	5	1	3	1	
#								
1	Manual assembly	H	L	M	L	L	L	52
2	Lean cells	M	L	H	L	L	L	64
3	Pilot line	M	M	H	M	M	M	84
4	Manual assists	H	L	M	L	L	L	52
5	High volume integrated assy	L	H	H	M	H	H	132
6	High volume stand alone assy	L	H	H	M	H	H	132

Table 1: The qualitative analysis for OUCHLS identifies the two automation options as the highest potential solutions.
KEY: L = Low contribution to success M = Moderate H = High

example, let's say our stakeholders told us that operational headcount, footprint and quality were the most important success criteria, while capital investment and ergonomics were less important. Using a qualitative tool like a Pugh matrix (Table 1), we can assign a weight to each success criterion, define what a great, acceptable and poor result would be for each criterion, and then score each of the preferred options.

To complete the assessment, we can review our evaluation with key stakeholders to make sure that we have not overlooked or unfairly assessed one of the options. Whatever the outcome, at this stage we must discontinue developing the less attractive options, regardless of how novel, exciting or promoted they are.

Optimise

Industrialisation plans generally involve some level of capital investment, so it is important to understand the financial implications of a given option. Return on investment (ROI) and payback period are standard metrics, but we can also consider the contribution to unit product cost associated with each preferred plan, which includes more than capital investment. Ongoing maintenance and operational costs, retooling costs, scrap value, poor performance, underutilised assets and other project lifecycle expenses can all be estimated and included in the financial analysis.

Additionally, scenario analysis will challenge the sensitivity of a plan or concept to changes in calculation inputs and assumptions. For example, for

> "Industrialising a product is less about planning for production and more about planning for success."

OUCHLS we may have identified a pilot line as the first step in the strategy, followed by a higher volume production line. However, after examining various demand forecast scenarios, we discover that the pilot line will be insufficient within several months. In order to meet the growing demand, we would need to be investing in the higher volume line in parallel. Therefore, the more fiscally responsible option is to jump straight to the higher volume solution. We also assumed that the manufacturing site would be in western Europe, so a highly automated solution would be justified. However, if new information suggests that the site will be in North Africa, a manual assist solution would have a stronger business case. It is normal to return to some original ideas or modify the current ideas in order to address some of these potential scenarios.

In addition to the financial analysis, executing a modelling or simulation exercise can build confidence in predicted throughput, material movements, replenishment activities and staffing levels. Simulations can also be developed into training and predictive tools for future changes. Another tool, animation, can be a powerful aid in demonstrating operational models to senior management, marketing departments and investors.

Recommend

At the conclusion of the optimise phase, we are in a position to recommend a path towards industrialisation. We have completed our planning, having:

- Identified product modifications that improve the likelihood of successful assembly
- Considered process and manufacturing risks and identified appropriate mitigations
- Investigated many different paths to production
- Narrowed our search to a few attractive options
- Rationalised the selection of a single path based on sound, quantitative analysis.

For best practices, we will document all of the work and our justification for proceeding with our recommended manufacturing strategy. We also need to ensure that our URS is updated to reflect all the new and additional requirements. This document will be key in soliciting proposals from possible suppliers and ensuring that we receive solutions that are compliant with our plan. At ATS, we use the URS documents that we receive as the basis for all solution proposals and then trace the requirements throughout the capital project to ensure that they are delivered.

PLANNING FOR SUCCESS

Industrialising a product is less about planning for production and more about

planning for success. A systematic review of product design, manufacturing process, scale-up and technology transfer risks and mitigations, key stakeholder requirements, production options and financial business case will result in a deliberated plan that everyone can align themselves with. Questions like the ones posed at the beginning of this article are limiting and presuppose a path to production, a path that can be costly without appropriate investigation. However, a path to a sustainable programme with quality production can be achieved by pursuing a disciplined approach like the one employed by ATS. Involve your key partners in the journey to ensure you have the optimal complement of skills and expertise to see the whole picture and arrive at the whole plan: a plan for success.

ABOUT THE AUTHORS

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.

Tom Hayes, PEng, is the Vice-President of Global Sales for the life sciences division of ATS Automation. He established the pre-automation capability at ATS early in 2000 before turning his efforts to global sales. Prior to his time with ATS, Mr Hayes held various operational positions within a global pharmaceutical and medical device company, culminating in the Vice-President North American Operations role, and then operated his own consultancy firm focused on innovative manufacturing solutions.

ABOUT THE COMPANY

ATS Automation is an industry-leading automation solutions provider to many of the world's most successful companies. ATS uses its extensive knowledge base and global capabilities in 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 in markets such as life sciences, chemicals, consumer products, electronics, food, beverage, transportation, energy, and oil and gas. Founded in 1978, ATS employs approximately 3,800 people at 20 manufacturing facilities and over 50 offices in North America, Europe, Southeast Asia and China. The Company's shares are traded on the Toronto Stock Exchange under the symbol ATA.

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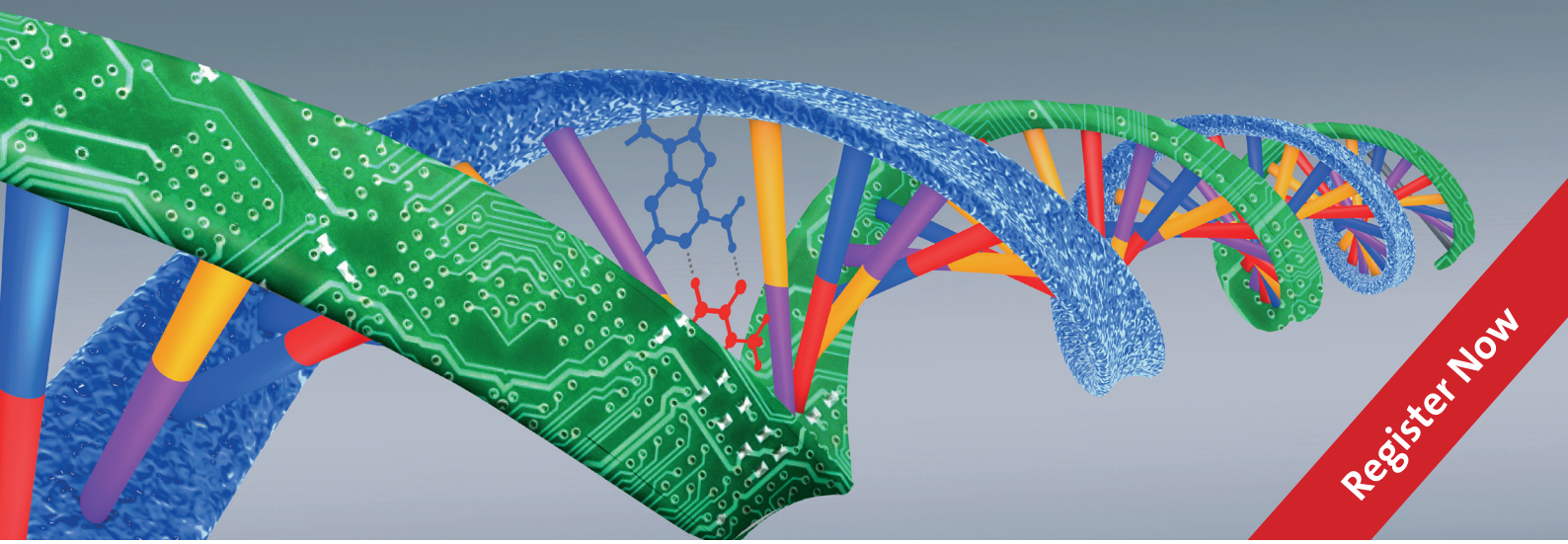

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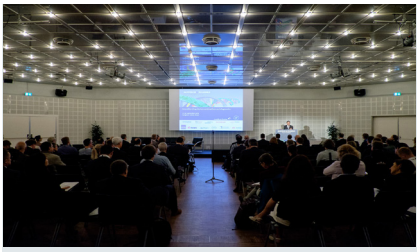

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MANAGING RISKS & COSTS FOR SEAMLESS SCALE-UP & SMOOTH COMMERCIALISATION

Today's drug delivery industry is seeing shifting thought in a number of areas, one of which is the move towards design for manufacture. Here, Simon Strothers, Director of Business Development, and Dave Seaward, PhD, Owner and Projects Director, both of 3P innovation, discuss a "better way" for developing drug delivery devices, highlighting design for manufacture, critical quality concerns and mandraulic prototyping.

INTRODUCTION

Much has been written on the use of quality by design (QbD) during the development of pharmaceuticals. The same principles can be equally applied to medical devices and drug/device combination products. This article describes a methodology for ensuring that QbD and design for manufacture (DfM) are considered in a pragmatic way at all stages of device development. The resulting medical products can be brought to market faster and at lower ongoing manufacturing costs. This methodology also ensures seamless scale-up between clinical supply and commercial volumes, using DfM, scalable production methods and agile project teams.

With an ageing population driving growth in the production of age-related therapies and drugs which can be self-administered, successful new product development (NPD) projects drive company growth and sustained competitive advantage. All industries have intrinsic NPD risks, whether they be considering

Typical medical device NPD risks	
Technical: "Will it work?"	Prototyping and clinical trials
Market: "Will it sell?"	Market studies, and/or voice of the customer interviews. For medical products, preliminary research to understand the reimbursement environment for the product is important and can vary significantly by region
Intellectual Property: "Freedom to trade?/Protected from copies?"	Patent searching and applying for patent protection
Regulatory: "Are we allowed to sell?"	Planning the submission process and preliminary discussions with regulators. For products that will be launched into regulated environments, regulatory acceptance of the product is critical
Supply chain: "Can we make it at an affordable price?"	Considering the manufacturing methods early within the product development. Prototyping the manufacturing process.

Table 1: Typical medical device NPD risks.

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the complexity of regulatory regimes, the requirement for clinical trials or within the supply chain. Ultimately the question is, can the product be made at an affordable price?

Unfortunately, the supply chain risk analysis and DfM are often left until late within the NPD process. These risks and some of the common ways of mitigating them are summarised in Table 1. DfM cannot be ignored, and the priority it is assigned at the early stages can make or break a project. The authors have observed two recurring reasons for the DfM oversight:

- Firstly, a lack of automation experience within device development teams, which are often clinically led, means the early-phase development team is unaware of the impact of their design choices on the ultimate cost of goods.
- Secondly, the "funding gap" (often referred to as the "valley of death") between initial research and commercialisation of a new medical device means that DfM is perceived as unaffordable. As a result, high costs can be incurred late in a development programme which would have been eliminated by a low cost investment earlier in the programme.

Overlooking DfM reflects a particularly short-term view, which is especially problematic in medical device development, where early product design decisions adversely "lock-in" high long-term manufacturing costs. Once clinical studies have been undertaken, there is a natural reluctance to change even minor product features to enable efficient production and reduce the cost of goods. The perceived and real need to repeat clinical studies with inherent timescale delays and additional costs prevent late product changes targeted at efficient manufacture. With an impending launch, which can repay significant R&D investment, the commercial decision is usually to move forward with higher than necessary costs of goods.

"Once clinical studies have been undertaken, there is a natural reluctance to change even minor product features to enable efficient production and reduce the cost of goods."

Ignoring DfM early in the product development lifecycle leads to higher than necessary costs of goods for the life of the product.

There is in fact a "better way" that can be applied to medical devices and combination pharmaceutical products.

QUALITY BY DESIGN & PROCESS ANALYTICAL TECHNOLOGY

This "better way" uses many of the concepts found within the pharmaceutical industry's trend towards QbD and process analytical technology (PAT). These in turn draw heavily on the experiences and methodologies developed within other industries, such as Six Sigma.

This change in mindset was due to the recognition by the US FDA that it has a remit to ensure the availability of safe, effective and affordable medicines. Traditional regulation and validation has been entirely focused on the quality of the end product, with little concern for the cost. In turn, this created the unintended consequence of inefficient and outdated manufacturing processes, which led to expensive medicines. The industry had been reluctant to introduce novel and more cost-effective manufacturing, or indeed to introduce any manufacturing change at all, due to a perception of regulatory uncertainty that was unfavourable for innovative manufacturing systems.

The regulatory framework changed in 2004 with the publication of the FDA's PAT Guidance. This has been supported with a number of guides produced by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The "Better Way"

Risks in all fields are best mitigated by recognising them early and proactively managing them. The following methodology identifies manufacturing risks early when costs and impacts of change are low. This leads to the early elimination of unfeasible options and development projects become easier to predict and forecast, both from a cost and schedule perspective.

To ensure any manufacturing process is efficient with low rejection levels, one must rely upon robust processes which operate well within their specifications – this is the essence of Six Sigma. The reader is introduced to the concept of "critical quality attributes" (CQAs), properties or characteristics of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality.

"Medical devices, like all products, can be considered as a number of sub-components that are brought together via a number of processes or unit operations."

Medical devices, like all products, can be considered as a number of sub-components that are brought together via a number of processes or unit operations. A unit operation can be considered as a process which performs a transformation as part of the route to manufacture the product. Depending on the medical device, these unit operations may include assembling, mixing, sealing, filling, coating, heating, gluing or a number of others. Every unit operation will have desirable and undesirable transformations that the process may generate – the manufacturing system will need to promote desirable transformations and eliminate (or identify and reject) undesirable transformations.

For example, a desirable transformation would be the clipping together of two plastic parts and an undesirable transformation is a mechanical clash leading to component damage – a simple lead-in within the design of one or both components can be the difference between a robust and a non-robust unit operation.

INDUSTRIALISING A NOVEL MEDICAL DEVICE THE AGILE WAY – CASE STUDY

3P's well-proven process development methodology adds value to its clients' medical device production to make the product successfully to specification, de-risking the manufacturing process using early-stage proof-of-principle work and allowing for easy commercialisation.

Let's consider a specific case study, a DfM collaboration between 3P and SteadyMed Therapeutics (San Ramon, CA, US). SteadyMed had developed PatchPump, a unique wearable device. 3P worked

with SteadyMed on the automation that manufactures the primary drug container, which is core to the technology.

The Product

The product is a patch pump device with a novel drug container, aseptically filled with sterile liquid drug at site of manufacture (Figure 1). 3P's involvement in the project was the development of the processes by which the primary drug container is made, tested for leaks and aseptically filled. The product specifications for the unique primary container (Figure 2) are:

- Volume: ≈2.5 mL
- Single channel for drug filling and air extraction
- Wide channel diameter designed to enable filling of viscous formulation
- Cyclo-olefin polymer (COP) multi-layer material membrane
- COP baseplate
- Blister-to-base sealing by impulse welding
- Septum sealing achieved by using ribs.

Product Development Challenges

There are many technical known-unknowns at the start of a new device development project, including:

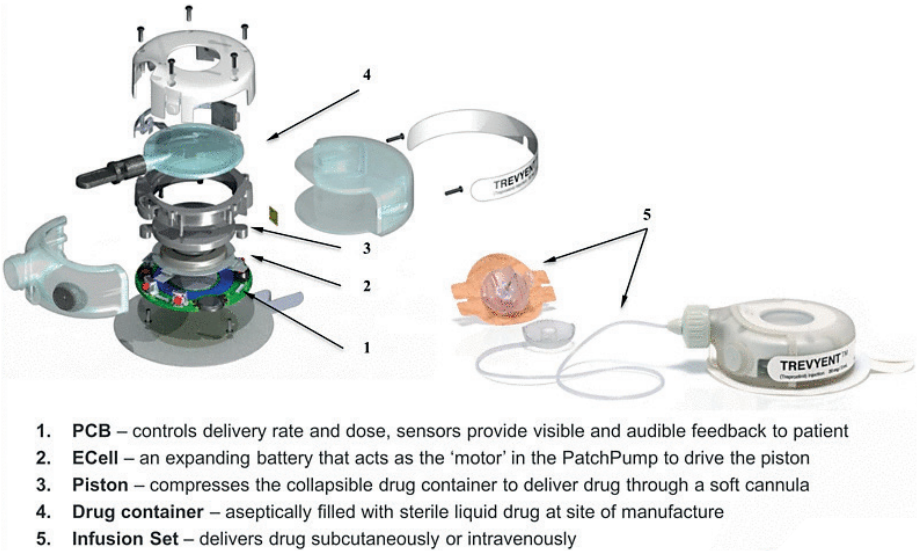
- What are the specific details of the device to ensure it functions perfectly?
- How to manufacture components?
- How to assemble components?
- How to fill the device?

Process Development Challenges

The key process risks and challenges identified included:

- How to form and seal a delicate blister?
- How to test the integrity of the sealed primary container?

> "In an ideal world, the interrelationship between all the CQAs and CPPs will be fully understood and described by formulaic relationships, however the real world is multi-dimensional with interrelationships which are often poorly understood."



1. **PCB** – controls delivery rate and dose, sensors provide visible and audible feedback to patient
2. **ECell** – an expanding battery that acts as the 'motor' in the PatchPump to drive the piston
3. **Piston** – compresses the collapsible drug container to deliver drug through a soft cannula
4. **Drug container** – aseptically filled with sterile liquid drug at site of manufacture
5. **Infusion Set** – delivers drug subcutaneously or intravenously

Figure 1: The components of SteadyMed's PatchPump.

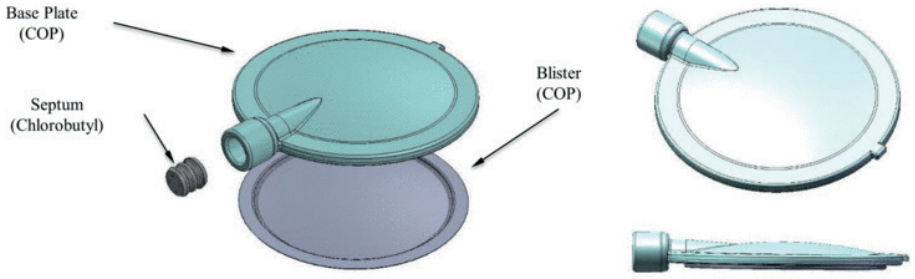


Figure 2: The primary container of SteadyMed's PatchPump.

- How to fill a semi-rigid product precisely?
- How to iterate and evolve the equipment with the process?
- How to manufacture the primary container?

The developed manufacturing process steps for the primary container are:

- Trays of baseplates fed in
- Reel of film loaded
- Robot transfer of baseplates into process module
- Pre-heat web
- Form blister with positive pressure
- Cut blister from web
- Weld blister onto baseplate.

A flexible COP film blister is heat welded to a COP injection moulded base plate. The expansion of a battery during discharge is used as a piston to dispense the drug precisely by moving the blister as required. Unique tooling is required to protect the blister whilst still generating a strong seal of the required dimensions. A novel multi-axis alignment system ensures uniform seal pressure and all processes are performed on a single axis to ensure accurate concentricity of the blister to the baseplate.

Production Development Challenges

The following were identified as the main challenges to be overcome for production scale-up:

- Filling the device
- Stopper seal area must not be contaminated (remain dry)
- Small aperture requires small-diameter filling needle, liquid has high velocity – target drugs have propensity to foam during filling
- Minimal headspace required
- Tight tolerance on head height
- Vacuum stoppering required
- Flexible membrane – variable volume, needs accurate control
- High accuracy required on fill volume.

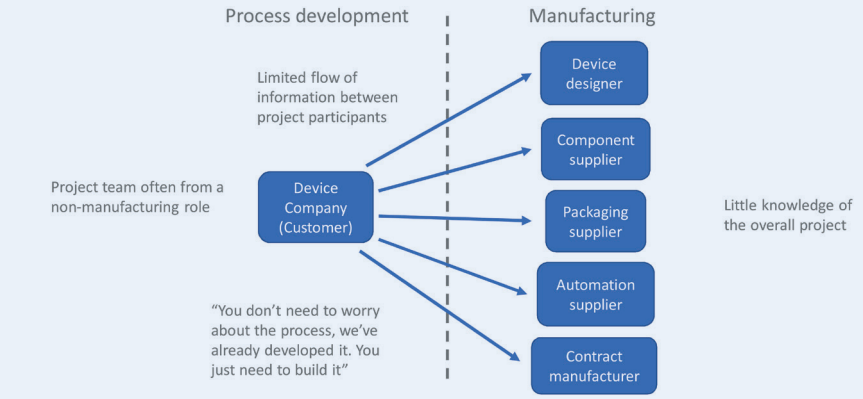
Customer Benefits

By partnering with 3P, the benefits to SteadyMed were:

- Innovative medical device to market quickly
- Low cost, robust process as risks identified early
- Custom-designed machinery (such as that shown in Figure 3).

BOX 1: AGILE PROJECT TEAM

1. Common Project Structure



2. Agile Project Structure

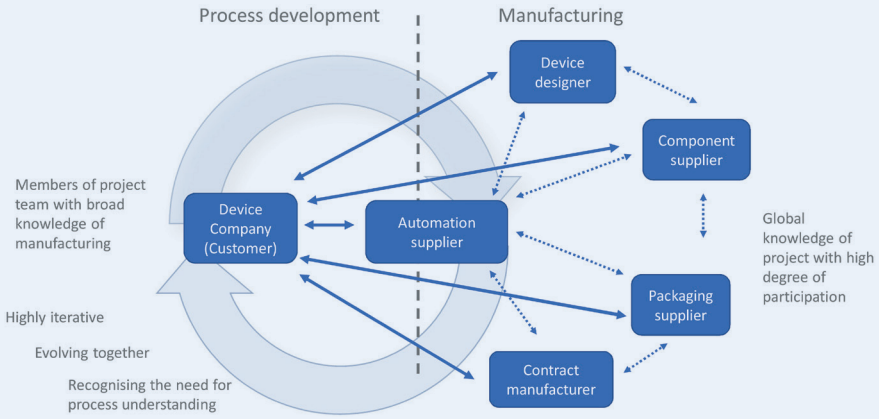


Figure 3: 3P is able to develop custom machinery for device manufacture.

AGILE TEAM STRUCTURE

The success of the SteadyMed project and overcoming product, process and production challenges successfully came down to the agile project team structure operated by SteadyMed and 3P. As opposed to the common project structure, the agile project structure allowed for the project team members from various suppliers, with a broad knowledge of manufacturing and used to highly iterative processes, to evolve together as one team (Box 1). The whole project team recognised the need for an end-to-end and seamless process understanding, ensuring global knowledge of the project and a high degree of interaction and unhindered communication between all facets of the project.

CRITICAL QUALITY ATTRIBUTES

As demonstrated by the case study, we can clearly see that the concept of critical process parameters (CPPs), i.e. independent process parameters (such as position, time, temperature, pressure, etc), is vital. CPPs need to be controlled in the production process as they are likely to have a significant impact on the CQAs.

In an ideal world the interrelationship between all the CQAs and CPPs will be fully understood and described by formulaic relationships, however the real world is multi-dimensional with interrelationships which are often poorly understood. This is especially the case if the process is associated with a novel product. A number of relatively simple and straightforward activities will significantly increase a team's understanding of product manufacturing processes. The activities also proactively identify any risks that need to be addressed.

In summary, the suggested activities are:

- Generate and then maintain a list of CQAs for the product. This list will evolve alongside the product development.
- Generate a list of all possible unit operations and ensure that any known tolerances and methods of measurement are also recorded. There will always be alternative processes with their own pros and cons, for example the choice between a clip, glue or a screw for binding two objects.
- List the inputs (product materials and components) and outputs (sub-assemblies and intermediaries) to each unit operation.

- Identify plausible ways of linking the unit operations together to form routes to manufacture. Ask if there are any methods of measuring and controlling the unit operation.
- Consider all the transformations the unit operations can generate (both intended and unintended transformations) – initially these can be subjective.
- Generate a table for each transformation and subjectively list the expected directional linkage between process parameters and transformations.
- Identify any likely CPPs that link to the CQAs.
- Generate and maintain a risk log. This should be continually updated (in such a way that all interested parties can record concerns).
- Identify what could be done to mitigate the risks.

PROTOTYPES TO MITIGATE RISKS & USING INSTRUMENTED AND SCALABLE PROCESSES

"Will it work?" risks for the product are mitigated by generating working models and prototypes, and then carrying out functional tests, and ultimately clinical studies. The increasing use of functional rapid prototypes has enabled product developers to test many different designs rapidly and cost effectively. What a decade ago took many months to accomplish can now be carried out in a few weeks, at low cost. There is an equivalent methodology for process development and DfM which involves prototyping the manufacturing process – rapid prototype can also be used to mock-up the assembly and manufacturing processes.

In any manufacturing system, there will typically be a number of machines linked together. Mapping and flowcharting these processes will provide an initial indication of the number and types of machine that may be required. Assembly machines for medical devices can vary in cost from several hundred thousand pounds to several million pounds each, which is well outside the reach of early-phase medical device development budgets. Any machine can, however, be considered as a sequence of unit operations. For any unit operation there are typically only a small number of machine parts interacting with the product, termed "end-effectors". If one considers a robot with a suction gripper, the end-effector is one low cost component (a rubber suction cup), which is manipulated via a high cost robot consisting of servo motors, gears, belts, ball-screws, framework, guarding, an electrical system and a control software.

> "3P has developed a method of identifying the critical end effectors and their motions and then building them into simple, manually-driven tooling."

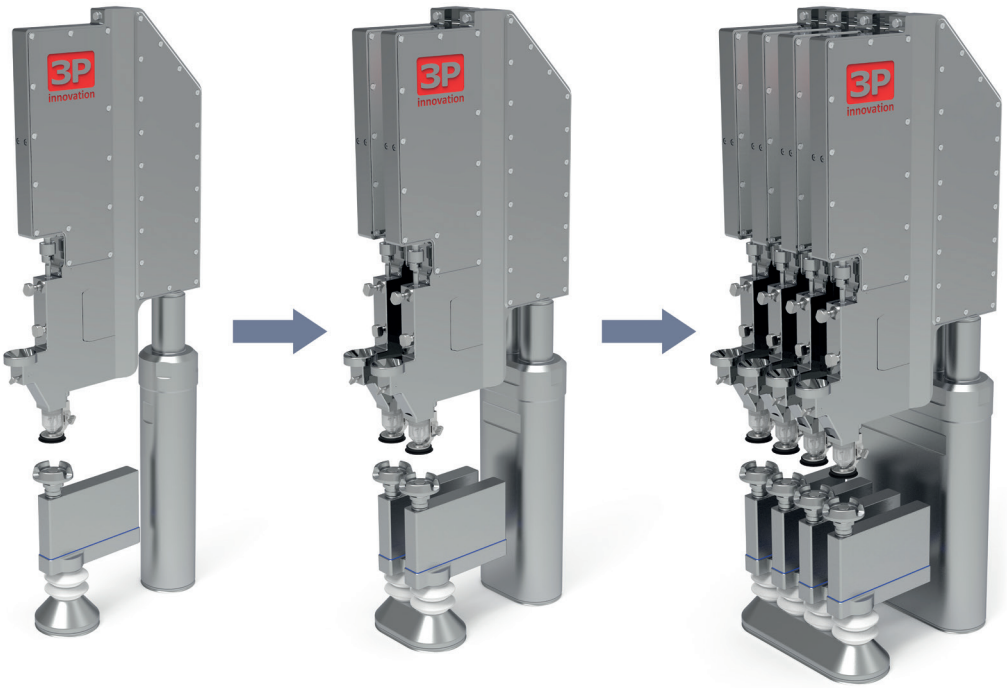


Figure 4: The Fill2Weight powder filling machine provides an example of the ability to scale by adding multiple units.

3P has developed a method of identifying the critical end effectors and their motions and then building them into simple, manually-driven tooling. Crucially, this is done in such a way that the process is scalable to the final commercial equipment. Initial consideration of techniques such as "poka-yoke" (a Six Sigma term, derived from Japanese, meaning a method that helps an equipment operator avoid mistakes) can also be introduced. Operators load and unload components into tooling (sometimes referred to as pucks or nests) and all subsequent actions are carried out by simple interfaces, such as levers and slideways, and powered by operators. Any specialist processing elements, such as sealing or gluing heads, can be mounted on the tooling.

Crucially, the operator is not normally allowed to perform the process directly, only indirectly via mechanisms. Such systems are often whimsically referred to as "mandraulic", "manumation" or "manumatic". Where specific process understanding is required additional sensors are added. For example, the real-time trace of force when two parts are clipped together can provide invaluable insight into the process robustness, the torque to activate a lever provides similar insights, and the pressure and flow can be used to detect leaks or to quantify the size of a small orifice. Process sensors can provide data to support product design changes, often very minor changes to component design can lead to significant improvements in product function and/or manufacturability.

One recent high-volume example saved 3P's client >£250,000 per week, via increases in production efficiency between an old product developed using traditional techniques and a new one developed using a 3P instrumented assembly fixture. This mandraulic approach is therefore ideal for initial low-volume sample making. For some projects it can prove so successful that multiple units are produced to enable rapid and low-cost manufacture of higher volume batches with more operators (Figure 4).

When positional tolerances are important, the tooling can be designed such that tolerances can be deliberately mis-set in a controlled manner. Using this methodology, process robustness can be determined and managed early within a product development lifecycle. This enables design of experiments (DoEs) which provide

process understanding. In QbD terminology the "design space" and "control space" can be determined. Thus, the standard deviation for CPPs and CQAs can be determined and the robustness of a given process assessed. It is not uncommon for unit operation processes to be initially found wanting. As mentioned prior, once a process is understood often only very simple changes are required to turn the process into a robust (six sigma) one.

Most medical devices contain a number of interacting injection moulded plastic parts. Initially, these will be rapid prototypes, then single-cavity moulds will be used for higher clinical volumes and finally multi-cavity moulds will be used for commercial volumes. It is normal to see wider dimensional variability from a multi-cavity mould than from a single-cavity mould. It is also normal to see differences in the mean dimensions with different coloured parts (the colourant, usually referred to as the masterbatch, changes the level of post injection shrinkage), i.e. parts of one colour may be dimensionally different to parts of another made from the same mould. By using mandraulic tooling early within a product development, process tolerances for this occurance can be identified at the outset. The most appropriate data features within components and sub-assemblies can be identified and, as before, minor changes made to accommodate them.

There are occasions where the motion profile of the end effector is a CPP in its own right. There are also occasions where very high volumes of samples are required beyond those that can be practically made via mandraulic systems, and yet which do not justify the investment in fully commercial, high-output systems. An intermediary solution between mandraulic and fully automatic systems exists in semi-automatic assembly. In a semi-automatic system, the operator loads components into tooling or a puck. The components in the puck can then be manipulated with a series of automatic (pneumatics, servo motors, robots, etc) or manual operations as required. As with the mandraulic solutions, additional sensors can be used to provide process understanding.

Many high speed commercial assembly systems use pucks to move components through a sequence of assembly stations. Frequently, commercial assembly machine companies will have an array of standard modules that can be placed over pucks. The pucks, end effectors and motion profiles are customised to each application. With knowledge of the target commercial machine, one key advantage of a semi-automatic system is its ability to fully replicate and mimic the process used in a commercial system, albeit at lower cost and throughput, although it is worth mentioning that whilst output speeds will be lower than the commercial system, the process speeds can be representative. Therefore, using a puck-based semi-automatic system eliminates scale-up risks between clinical- and commercial-volume manufacture whilst providing a cost-effective route to clinical production capacity.

The implementation of this methodology ensures that medical devices are developed with the needs of manufacturing from the outset. This in turn leads to high-efficiency, high-quality processes with low rejection rates, all of which lead to a low cost of goods. The prototype manufacturing systems also provide the additional benefit of a cost-efficient method of producing initial low volumes of samples for clinical trials.

CONCLUSION

Medical device developments often ignore design for manufacture, resulting in inefficient commercial production and relatively high costs of goods. The authors propose a "better way", whereby the requirements of automation are considered early within the medical device development process. This provides a low cost method of providing clinical samples from a scalable process. All of which leads to lower ongoing costs of goods.

ABOUT THE COMPANY

3P innovation, the home for Product, Process and Production innovation, is a successful engineering company with a reputation for delivering innovative solutions to major pharmaceutical, medical and fast-moving consumer goods companies. The company develops custom automation, usually associated with product launches. Its approach ensures robust products are manufactured on efficient machines. From low speed laboratory equipment to high speed assembly lines, 3P can develop an appropriate custom solution. It also has a range of standard machines, products and technologies. All 3P's standard systems have been designed to reduce the time to market associated with new product developments.

ABOUT THE AUTHORS

Simon Strothers joined as Director, Business Development, of 3P innovation in 2013 and is responsible for Business Development and Marketing. His background is in mechanical engineering. He qualified with a Bachelor's degree in Mechanical Engineering at the University of Manchester (UK) and has a Masters Degree in Business Management from Warwick University (UK). Mr Strothers' career started with Lucas Aerospace, where he worked as Design Engineer, Systems Engineer and Programme Manager, responsible for flight control and engine actuation systems for aircraft. He then worked as a management consultant for four years, driving business improvement projects across a wide variety of industries including paper making, railways and aerospace. For the past 18 years he has worked in the field of custom automation and engineering consultancy for the life sciences and FMCG sectors, initially as senior project manager and since 2006 as business development director.

Dave Seaward, Owner and Projects Director of 3P innovation, is a chartered engineer with a first degree in joint electrical and mechanical engineering and a control theory PhD. His PhD focused on the application of servo motors to packaging machinery. This early work has led to a career spanning 30 years associated with the development of custom automation for a variety of industries. These include the pharmaceutical and medical device sectors. Many of his projects have included advanced powder or liquid dispensing. Seaward is named inventor on multiple patents. He has worked on 14 dry powder inhaler programmes and nine different injectable drug delivery and autoinjector projects. At 3P, he developed high-speed gravimetric powder dispensing technology capable of dosing pure API including biologics into devices and capsules for inhaled and injectable applications. More recently he has helped develop the processes to manufacture a number of drug-eluting polymer/modified-release products.

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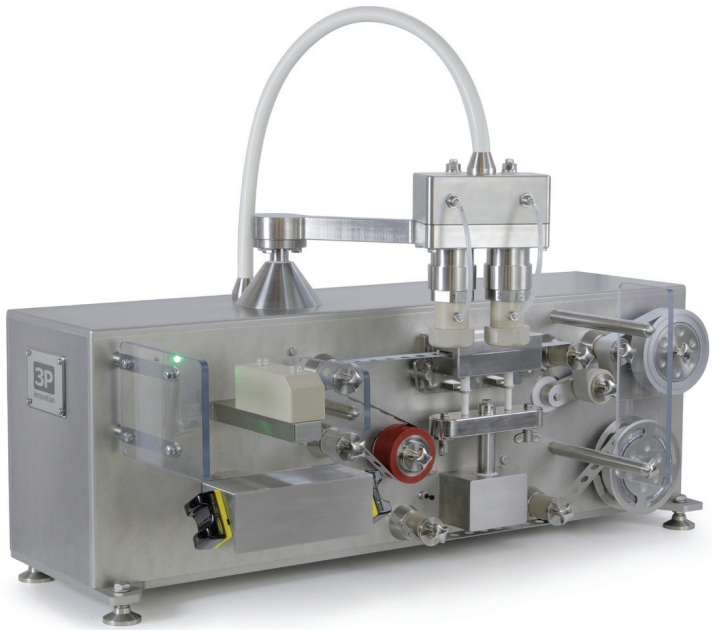

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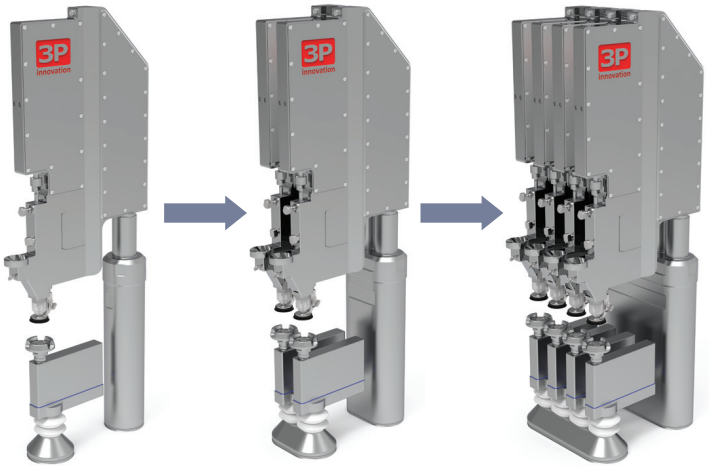

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KEY CONSIDERATIONS FOR ACCURATE QUANTIFICATION OF SUB-MICRON PARTICLES IN PHARMACEUTICALS

In this article, Jean-Luc Fraikin, PhD, Chief Executive Officer of Spectradyne, discusses the use of resistive pulse sensing as a method to characterise nanoparticles in biologic formulations. Spectradyne has developed a new implementation of this technique, MPRS, that makes it a practical analytical method for industrial pharmaceutical applications.

INTRODUCTION

The therapeutic and diagnostic applications of biological materials are proliferating, including antibodies and antibody drug conjugates for direct therapeutic delivery, viruses for delivery of novel gene therapies, and extracellular vesicles for delivering complex therapeutic signalling agents. Significantly, each of these classes of material includes a key component with dimensions in the nanometre scale, in some cases including the delivery vehicles themselves, and in many cases unwanted aggregates. Quantification of both desired and spurious nanoparticle components in these materials is critical, at all stages of development, to properly evaluate efficacy and ensure product safety. Accurate physical characterisation of biological nanoparticles in the sub-micron size range is therefore an increasingly important requirement for the drug delivery industry.

The intent of this article is to clarify the key considerations for the proper measurement of sub-micron particles near an instrument's limit of detection, shed light (pun intended) on certain inherent limitations of optical particle characterisation technologies, and provide a reference for researchers facing these kinds of measurement challenges in the drug delivery industry.

> "The accurate measurement of sub-micron particles, in general, becomes increasingly difficult as they decrease in size."

ACCURATE MEASUREMENTS OF BIOLOGICAL NANOPARTICLES

The accurate measurement of sub-micron particles, in general, becomes increasingly difficult as they decrease in size and their measurement signals are reduced to the detection limits of the measurement instrument. While cryo-transmission electron microscopy (CryoTEM) remains the gold standard for sizing nanoscale particles, and this technology's sub-nanometre sizing resolution makes it very powerful as an occasional analytical tool, the cost and slow speed of this technique render it unsuitable for routine use. Historically, the most commonly used particle measurement technologies for the sub-micron size range have been optical techniques such as dynamic light scattering (DLS), nanoparticle tracking analysis (NTA) and flow cytometry (FC).

Biological nanoparticles however have three common characteristics that make them exceptionally difficult to measure using optical techniques, primarily because these measurements rely on detecting light scattered from these very small particles.

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"Non-optical techniques for measuring nanoparticle size and concentration provide a powerful alternative to these optical techniques. The most ubiquitous is based on an electrical measurement technique known as resistive pulse sensing."

First, the intensity of the scattered light decreases dramatically as the particles get smaller, scaling with a sixth-power dependence on diameter.[1] A 100 nm particle therefore scatters one million times less light than a 1 µm particle. This dependence, coupled with the finite dynamic range of optical sensors, limits the practical range of sizes that can be measured in a single sample and makes detection of small particles significantly more challenging.

Secondly, the physical composition of most biological materials results in a particle index of refraction that is similar to that of the surrounding, typically aqueous, media, in some cases with indices that differ by only a few percent. The scattered light intensity is proportional to this index difference (also called contrast), so can result in another reduction of the signal by a factor of 10 to 100. The combination of low index-contrast and small size significantly weakens the intensity of light that scatters from biological nanoparticles, thereby limiting the sensitivity of optical measurement techniques to these sub-micron particles.

Finally, the complex origins of biological nanoparticles (e.g. aggregation processes or shedding from cells) yield real-world samples with diverse material composition and a broad range of particle sizes. The high degree of size polydispersity in these samples places a significant burden on sizing resolution in the case of NTA, which measures scattered light from single particles, and presents an insurmountable obstacle for DLS, which performs an ensemble measurement of all particles in the incident light path and cannot tolerate significant polydispersity.

Non-optical techniques for measuring nanoparticle size and concentration provide a powerful alternative to these optical techniques. The most common is based on an electrical measurement technique known as resistive pulse sensing (RPS), historically referred to as the Coulter principle after the inventor of the technique, Wallace Coulter.[2] RPS is a well-proven technique for measuring the size and concentration of large particles (>1 µm) and has been the gold standard for decades for whole-blood cell counting.

RPS is ideally suited to the measurement of biological nanoparticles for three reasons:

1. The detection signal scales linearly with particle volume, so the dynamic range of sizes that can be measured in a single sample is much larger.
2. RPS measurements are independent of the material composition of the particles, and therefore do not suffer from the same loss of sensitivity as optical techniques.
3. Because particles are measured individually with high precision in RPS, high polydispersity is not a significant issue. It is possible to perform particle measurements directly in complex media, such as serum, urine and other biological fluids whose polydispersity would otherwise confound light scattering techniques.

So why has the use of RPS historically been limited to large particles alone? RPS requires that all particles to be measured pass through a physical constriction for detection, and the size of this constriction must be decreased in order to detect smaller particles. Real-world samples contain a significant concentration of particles that are larger than the small constriction size required for nanoparticle measurements. Therefore, in the simplest implementations of RPS, the large particles in the sample cause frequent blockages of the constriction and prohibit practical use of the technique.

In 2009, in an early attempt to circumvent this obstacle, Izon Science (Christchurch, New Zealand) developed the qNano for RPS measurements. Izon's implementation set the constriction in a deformable membrane ("Tuneable" RPS) that could be adjusted to allow blockages to pass through before resuming measurements. While the technology has been cited in a number of academic publications, its deployment has been limited in industrial applications that demand high throughput and turnkey operation.

More recently, Spectradyne has commercialised a different approach to RPS that significantly improves the practicality of the technique for routine nanoparticle analysis of real-world samples in an industrial context.[3] Spectradyne's nCS1 instrument is a microfluidic implementation of RPS (MRPS) and leverages manufacturing techniques from the semiconductor industry to incorporate a number of fluidic features in a disposable analysis cartridge that permits nanoparticle analysis while significantly reducing blockage events. MRPS enables straightforward measurements of highly polydisperse biological nanoparticle samples such as protein aggregates, serum, urine and crude preparations of extracellular vesicles, and is seeing adoption by prominent researchers in the pharmaceutical industry.[4]

Regardless of an instrument's underlying principle of operation, all instruments are eventually limited by their intrinsic sensitivity and noise. But as biological nanoparticles increase in importance in the drug delivery industry, regulators such as the US FDA increasingly recognise the importance of using a complete set of characterisation methods, as stated by Susan Kirshner, PhD, in a 2012 talk entitled, "Regulatory expectations for analysis of aggregates and particles", including methods that are orthogonal to conventional light-based techniques. MRPS represents a practical and easy-to-use alternative that satisfies these regulatory expectations.

MEASUREMENT EXAMPLES

Three measurement examples are presented below that illustrate the importance of the above considerations in real-world drug delivery industry applications. First, measurements of a simple extracellular vesicle preparation using three different particle analysis methods (NTA, CryoTEM and MRPS) are compared to show the importance of using orthogonal measurement techniques. Second, an aggregated protein sample is measured by NTA and MRPS and illustrates how the instrument limitations described above apply to a different class of sample. Finally, measurements of a series of stressed protein samples are used to demonstrate how the smaller particle detection limit of MRPS enables earlier detection of protein aggregation.

Example 1: Extracellular Vesicles Three Ways

Unless they are carefully purified, samples of extracellular vesicles (EVs) naturally exhibit an approximate power-law distribution of particle concentration versus particle size.[5] Such a broad particle size distribution provides an excellent opportunity to evaluate the sensitivity of different measurement techniques over a comprehensive size range in a relevant sample type. For this measurement example, a simple sample of EVs from human cell-free urine was analysed using MRPS, NTA, and CryoTEM (Figure 1).

MRPS shows a clear power-law dependence of concentration on particle size that extends down to 50 nm, the limit of detection for the analysis cartridge used in this measurement. Importantly, the MRPS measurements are in excellent agreement with those of CryoTEM, the gold standard for measuring size and relative concentration of particles in this type of sample.

The NTA measurement results highlight the limitation of the NTA technique for detecting small particles in this type of sample. NTA significantly under-reports the concentration of smaller particles, with a divergence from the CryoTEM result becoming apparent, starting at 200 nm and increasing dramatically below about 150 nm. The discrepancy between NTA and CryoTEM expands to several orders of magnitude below 150 nm diameter.

Researchers must therefore take care when interpreting NTA data such as these, especially as the resulting profile appears to indicate the presence of a peak in the size distribution around 150 nm, which is not a real feature of the particle size distribution. The peak can be accurately identified as an artefact of the measurement technique only when orthogonal methods such as MRPS or CryoTEM are used for comparison, as in this example. Unfortunately, inaccurate optically-based measurements of EV size distributions, such as this NTA measurement, appear often in the literature and are not generally supported by orthogonal techniques such as MRPS or CryoTEM.

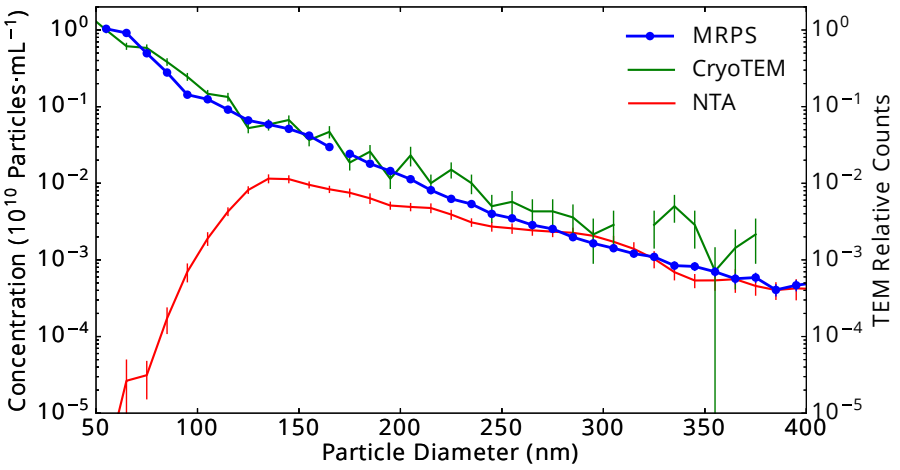

Figure 1: Extracellular vesicles isolated from human serum measured using three orthogonal techniques: MRPS, CryoTEM and NTA. The loss of sensitivity of the optical technique to small, weakly-scattering biological nanoparticles becomes apparent when compared with orthogonal techniques such as MRPS and the gold standard, CryoTEM.

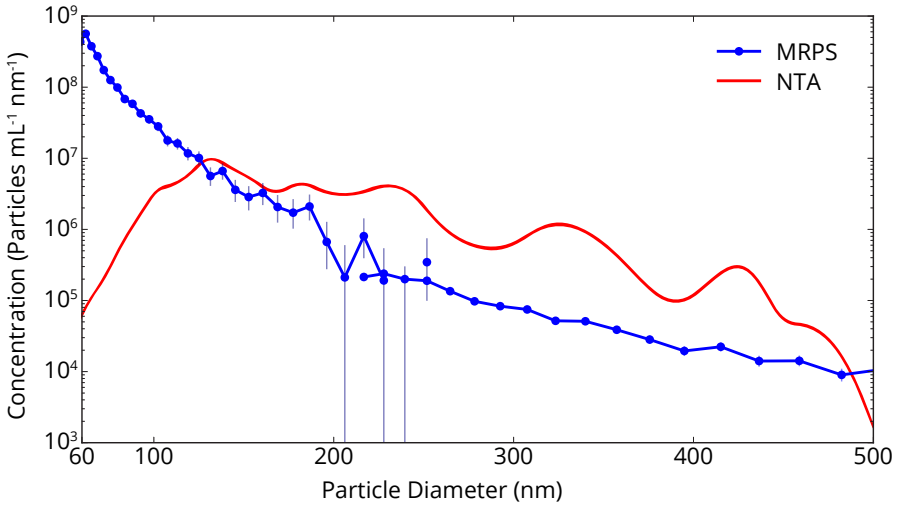

Figure 2: Protein aggregates in a stressed sample show the expected power-law dependence of concentration on size when measured by MRPS. The size range of sensitivity of the NTA is apparent as the method underreports concentration outside approximately 150–450 nm diameter.

> "Accurate and precise measurements of smaller biological nanoparticles, such as those obtained with MRPS, enable significant time savings for real-world drug delivery applications."

Example 2: Protein Aggregation

In the process of aggregation, protein monomers a few nanometres in diameter aggregate into dimers, trimers and subsequently into larger particles that can grow to be as large as tens of microns in diameter. This process generates a highly polydisperse mixture that contains particles spanning many orders of magnitude in diameter and concentration, with an approximate power-law distribution of aggregate concentration versus particle size.

In this specific example, a proprietary protein sample was prepared at 5 mg/mL in phosphate-buffered saline and was stressed at elevated temperature for 24 hours to accelerate the aggregation process. The particle size distribution in the sample was measured by NTA and MRPS (Figure 2). The MRPS measurements show the expected power-law dependence of concentration on size, and further indicate that the power-law dependence extends down to at least 60 nm, which is the small size limit of detection of the analysis cartridge used for this measurement.

The sensitivity limitations of the optical technique are clearly illustrated in this example as well. While NTA readily detects particles in the sample between about 150 nm and 450 nm, below 150 nm the concentration reported by NTA decreases sharply (note the log scale on the vertical axis), likely because of the very dramatic

reduction in scattering intensity for these smaller protein aggregates. Due to this spurious apparent decrease in concentration versus size, the data could be incorrectly interpreted as indicating a peak in the size distribution. Without using an orthogonal technique such as MRPS to verify the true nature of the particle size distribution, the unwary researcher may be led astray.

Example 3: MRPS Enables Earlier Detection of Protein Aggregation

Accurate and precise measurements of smaller biological nanoparticles, such as those obtained with MRPS, enable significant time savings for real-world drug delivery applications. In this example, MRPS was used to quantify protein aggregates in stressed drug formulations. The results show that stress-induced aggregation can be detected significantly earlier in the process by detecting and analysing concentrations of smaller particles.

Aliquots of a proprietary biologic drug formulation were stressed for times varying from 0 minutes (control) to 60 minutes, with MRPS subsequently used to quantify aggregates in each sample (Figure 3). The data show the expected trend very clearly: as the amount of stress applied to the samples increases, the concentration of aggregates in the sample increases across all particle sizes.

Importantly however, aggregate concentration increases first at small particle sizes and later at large sizes. This effect is apparent in the data, as shown in the inset to Figure 3. When the concentration is measured on the subranges R1 to R3 (small particles to large, respectively), the effect of stress on the sample is apparent in R1 at the first time point, taken after just 10 min. This behaviour is consistent with expectations, since protein aggregates must start small before growing to larger sizes, and presents a significant opportunity to save time in formulation development.

Using accurate methods for quantifying smaller nanoparticles such as MRPS, formulation stress tests can be performed in a fraction of the time that would be required using optical techniques that lack sufficient sensitivity to detect the smaller, earlier-stage, aggregates. In an industrial environment, the ability to obtain this data both faster and earlier in the process can lead to a significant increase in process efficiency.

CONCLUSION

As therapeutic and diagnostic applications of nanoscale biological materials proliferate, their accurate quantification becomes increasingly important. This article demonstrates that, while ubiquitous, optical methods for nanoparticle analysis must be used with a complete understanding of their limitations, and conclusions should be supported by results from orthogonal measurement techniques. The cited examples illustrate how artefacts resulting from the sensitivity limitations of optical techniques can misrepresent the true composition of complex biological nanoparticle samples. The examples also show that practical techniques, such as MRPS, are capable of accurate quantitative measurements of sub-micron biological particles and offer an opportunity for significant savings of time and money in real-world pharmaceutical industry applications.

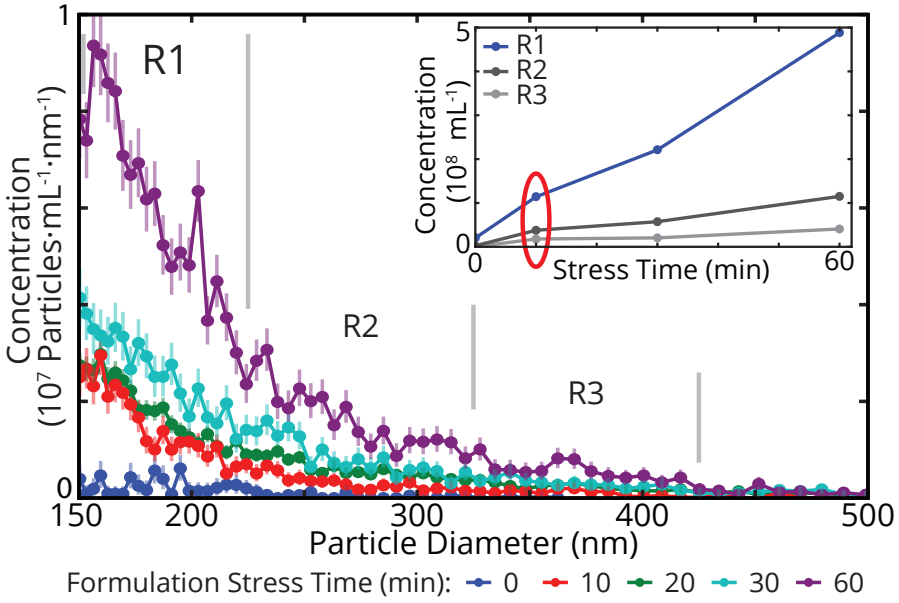

Figure 3: Protein aggregates in a stressed sample show the expected trend of increasing concentration with increasing stress. Concentration measurements on three subranges of particle size (inset) demonstrate that the effect of stress on the sample are detected earlier by quantifying smaller aggregates.

ABOUT THE COMPANY

Spectradyne develops innovative analytical technologies with a focus on delivering accurate measurements of particles in the submicron size range. The company operates across a broad set of industries, including pharmaceuticals and nanomedicine, cosmetics and semiconductor processing.

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Jean-Luc Fraikin is Chief Executive Officer and a co-founder of Spectradyne. Dr Fraikin obtained his PhD in physics from the University of California, Santa Barbara, where he studied electrical sensing in fluidic systems and particle analysis. He also received postdoctoral training in biochemistry and cancer cell biology and developed microfluidics-based diagnostics in industry before co-founding Spectradyne.

ORAL THIN FILMS: NOVEL MANUFACTURING TECHNOLOGY & ITS CHALLENGES

Presented from both the technology and formulation perspectives, here, Nidhi Prakash Sapkal, PhD, Principal Research Co-ordinator, and Anwar Siraj Daud, PhD, Managing Director, both of Zim Laboratories, discuss the challenges of industrialising oral thin films, a promising but difficult dosage form.

INTRODUCTION

In the last decade, oral thin films (OTFs) have been gaining widespread acceptance as a drug delivery solution amongst pharma manufacturing companies. These films have significant visual and functional differences from the other solid oral dosage forms, such as tablets and capsules, and thus provide strong product differentiation. The fact that these films disintegrate and dissolve in the mouth makes them particularly desirable for certain patient groups, such as paediatric, geriatric, dysphagic and bed-ridden patients. Table 1 describes some such patient populations and their specific needs.

Thin films are an innovative technology platform that is amenable to a wide product range. Many molecules, across various therapeutic segments, can be developed in this form. It provides immense benefits for the intended patients, clinicians, carers and other stake holders, such as those in the supply chain. Table 2 lists the benefits of OTF technology to various stakeholders.

> "Pharmaceutical thin films can be manufactured by using either solvent casting or melt extrusion. At present, commercially available films predominantly use solvent casting."

Patient Type	Examples of Specific Needs and Problems
Paediatric	• Uncooperative patients • Prescribed liquids as they can't swallow pills • Liquid formulations are associated with administration of imprecise doses • Liquids have handling, storage and transport problems
Geriatric	• With increasing age, swallowing is more difficult • Because of many chronic problems, pill burden is high • Dependent upon caregiver
Dysphagic	• Inherent difficulty in swallowing
Suffering from neurological disorder	• Uncooperative patients • Voluntary swallowing absent • Tendency to spit out the medicines
Bed ridden	• Difficult to sit in upright position to consume water • Dependent upon caregiver
Nauseous because of other primary problems like emesis, migraine	• Consumption of water, or anything, potentiates nausea and triggers emesis • Medication with rapid onset of action is highly desirable
Suffering from urology related problems, or anorexic	• Consumption of water leads to worsening of symptoms like increased diuresis or reduced appetite.

Table 1: Problems and requirements of different patient groups which drug delivery can address.

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Table 2: Benefits of OTF Technology to the various stakeholders.

TECHNOLOGICAL CHALLENGES

Pharmaceutical thin films can be manufactured by using either solvent casting or melt extrusion. At present, commercially available films predominantly use solvent casting. With this method, a solution of hydrophilic polymers and other functional excipients is deposited on a substrate in predetermined thickness. This wet film is then dried; in the literature, there are reports of bottom drying, top drying, alternate-surface drying or a combination of all such processes. Several variations in this basic method have been proposed in the literature in order to get stable films with desirable characteristics, but not all of them have the potential for industrialisation. Some novel methods of manufacturing of OTFs with novel attributes are discussed here along with challenges involved in their industrialisation.

Fuisz and Fuisz

Fuisz and Fuisz[1] describe a single-layer film with the benefits of a double-layer film. The product obtained using their method exhibits different dissolution behaviours from each side of the film. The product can be used for buccal or sublingual administration where drug release from one side of the film is desirable. The method has advantages over methods of manufacturing double-layer film, where two films are manufactured separately and then placed together.

Here, the difference in dissolution is achieved by adding a hydrophobic material of different density than the other film-forming materials. Such a dispersion, upon deposition to a support surface, shows sedimentation of the hydrophobic material in the thickness direction of film. The extent of sedimentation will depend upon the time the wet film is kept undisturbed before drying.

In the course of industrialising this invention, a major challenge will be critical control of process parameters to obtain films of consistent quality. Since the hydrophobic material is meant to sediment upon layering of the film, it will also tend to sediment during the dispersion stage before layering, therefore continuous stirring is recommended for such dispersions during manufacturing. However, the stirring process will have an impact on the particle size and hydrophobicity of functional materials. This will further affect uniformity of the final films and their intended dissolution profiles. This challenge will be particularly significant for large commercial batches, as process durations will be long.

Vrbata

Vrbata[2,3] described an electrospinning method for producing nanofibre-based fast-dissolving films. Such films are very interesting as they offer advantages of both nanotechnology and thin films in one delivery system. They have demonstrated higher solubility and improved bioavailability. These films therefore have significant advantages over currently available OTFs.

Currently reported techniques for manufacturing of nanotechnology based films involve making nanoparticles separately and then putting them in a film-forming dispersion. The method described by Dolezal is a single-step process which, though highly useful, poses several challenges to industrialisation when looking to produce product of consistent quality. Uniformity in nanofibre dimensions at large scale would require an unfluctuating voltage, and consistent spray rate and substrate speed, along with many other factors.

Moreover, the dose uniformity in the film is directly controlled by spray pattern. Maintaining such strict control of spray pattern is a challenge. The electrospinning process involves deposition of nanofibres on a conductive surface. Many pharma-grade substrates are not conductive in nature and thus will interfere with the electrospinning process. All these challenges need to be addressed before industrialisation of this delivery system.

Monitoring OTF Manufacture

OTF manufacturing is, in general, an in-line process with a short manufacturing cycle, therefore critical monitoring of all the process parameters is very important. There are many differences to the in-process monitoring controls and off-process testing compared with conventional dosage forms. For instance, in the case of tablets, uniformity in weight is important, whereas for OTFs uniformity in thickness is an important parameter. The controls are devised to monitor change in film thickness during various stages of casting.

In case of tablets, moisture content needs to be determined only once after granulation, but in OTFs, strict monitoring of moisture content is required during all stages of processing as this determines shelf life of the product in a significant way. Higher than the desired moisture content may lead to chemical instability of the active ingredients, while lower than the desired moisture content may make a film brittle. In summary, the technological challenges are:

- Availability of manufacturing equipment compatible with the technology
- Obtaining robust manufacturing process: high-speed manufacturing of consistently uniform product for long batch runs
- Criticality of online process monitoring due to short manufacturing cycles
- Modification of analytical testing equipment and methods
- High-dose drug loading can interfere in the film formation
- Size and weight can't be increased beyond a limit.

Melt Extrusion

Melt extrusion is not useful for manufacturing of thin films as the films obtained are not as fast dissolving as those obtained using solvent casting. In this process, the polymers suitable for the melt extrusion process are melted in the presence of other ingredients and subsequently extruded in the shape of films. Because of this melt-solidification process, polymers exhibit varied film forming properties. Additionally, thermo-labile APIs can't be processed using this technique. This is the reason that melt extrusion is not popular for commercial manufacturing of OTFs.

FORMULATION CHALLENGES

There are formulation challenges unique to OTFs due to increased moisture content, high drying temperatures and overall weight constraints. The properties of the film critically depend upon the properties of the drug molecules, such as hydrophobicity, bulk density, solubility and particle size.

Many APIs have been found to interact with film-forming materials that modify their casting behaviour and processability. It has been seen that for the same film-forming composition, different APIs at the same dosage level and with similar processing conditions result in films with different properties, including solubility, tensile strength, percent elongation, disintegration time and disintegration behaviour in the mouth. This is because these APIs interact differently with the same film-forming composition, therefore altering the OTF properties.

> "Since the attraction to this dosage form derives from its low weight and uniform thinness, these cannot be compromised in any way during development."

On the other hand, drug molecules have also been found to show different physicochemical properties with different film-forming polymers. APIs like ketorolac tromethamine and levocetirizine have been found to exhibit different polymorphic forms when processed with different film-forming polymers. Needless to say, such behaviour affects product stability drastically. Studies have revealed that, for the same polymeric composition, different drying temperatures of the films not only affect folding endurance, tensile strength and stability of the APIs but also their release behaviour. This happens because of a change in the nature of interactions between the drug and polymer at different temperature.

Another major challenge lies in the development of taste-masked films for bitter APIs. There are several taste-masking techniques, however these taste-masked complexes or intermediates further interfere with the film-forming properties of polymers and pose challenges to developing films with the desired attributes. Challenges also lie in selecting the number of enabling excipients that can be used as solubility enhancers, taste modifiers and stabilisers. It is worth remembering throughout that, since the attraction to this dosage form derives from its low weight and uniform thinness, these cannot be compromised in any way during development.

CONCLUSION

In general, the manufacture of fast-dissolving OTFs is a very challenging process. As mentioned in the beginning of this article, there are several techniques disclosed in the literature that result in OTFs with novel and advanced features. However, converting those techniques into usable technologies is a real challenge. This is the reason that there are presently very few products in the market that are manufactured using such techniques.

ABOUT THE COMPANY

Zim Laboratories is an innovative drug delivery solution provider focusing on improving patient convenience and adherence. It offers a range of technology-based drug delivery solutions and non-infringing proprietary manufacturing processes for production and supply of innovative and differentiated generic pharmaceutical products. Zim manufactures a comprehensive range of value-added solid dosage products in semi-finished and finished categories. These include granules, pellets (sustained, modified and extended release), taste-masked powders, suspensions, tablets, capsules and its recently developed oral thin films.

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ABOUT THE AUTHORS

Dr Nidhi Sapkal is Professor at Gurunanak College of Pharmacy and Principal Research Co-ordinator at Zim Laboratories. She started her career 21 years ago as an academic. At Zim, she is actively contributing to R&D involving novel products and process technologies. She leads various activities related to new product development involving thin film technology including project management, intellectual property, clinical and regulatory. Dr Sapkal has about 25 research papers and 20 patent applications to her credit, and has delivered many lectures at international conferences.

Dr Anwar Daud, MPharm, PhD, is Managing Director of Zim Laboratories. He established the company in 1989 and is responsible for the vision and overall growth strategy of Zim. He leads the R&D function and export business of the company. A keen student of pharmaceutical process innovation, his work in several spheres of R&D has resulted in a number of pharmaceutical manufacturing process patents and research publications. He is a mentor at many educational institutes, a proactive member of several professional bodies, and a distinguished speaker.

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THE BIGGEST MISTAKES COMPANIES MAKE COMMERCIALISING DRUG DELIVERY – AND WHAT TO DO ABOUT THEM

Successfully scaling-up a product to industrial production is challenging, but is even more challenging if design fundamentals are not incorporated into the development process. In this article, Beth Blackburn, Director of Systems Engineering, Ximedica, details the pitfalls and potential solutions in setting down requirements early in device development to ensure a product's successful commercialisation.

Early-stage companies have many dragons to battle, particularly in drug delivery. They are fundraising, filing IP, finding suppliers and creating a physical product for the first time. Additionally, they are developing both pharmaceuticals and medical devices, and therefore are navigating the treacherous regulatory and reimbursement pathways for both.

> "With so many difficult tasks to complete, companies often skimp on developing solid requirements for their drug delivery devices."

With so many difficult tasks to complete, companies often skimp on developing solid requirements for their drug delivery devices. Requirements tie together the user needs and the system design in a quantifiable and traceable manner, otherwise referred to as design inputs. Many activities associated with developing clear requirements are out of the scope of the actual technology or invention, and many are expensive. That combination makes it is easy to ignore some of the fundamental principles in device development. However, ignoring them can cost companies more than they often imagine.

WHY DO COMPANIES SKIMP ON GOOD REQUIREMENTS?

There are good reasons companies might drop the ball on developing requirements for drug delivery devices. A lot of early-stage companies think, "We've created a product, we've created some stir, we've gotten funding, we have something that's pretty clear. Let's just go."

That concept that "if we build it, they will come" can lead companies down an unsuccessful commercial path. Furthermore, just because the product is clear to the early-stage company doesn't mean it doesn't require documentation. Requirements development can take time. Moreover, the skills associated with developing clear requirements for drug delivery devices are often unfamiliar to an inventor or a CEO of an early stage company.

Requirements development is the most overlooked aspect of product development, even among companies that have been around a while, maybe even having some products on the market. It is tempting to think that if a company builds several instruments out of the same parts, in the same way, they are in the clear. However, it is important to take time to understand the design, variability in how one change can impact the rest of the design, and how individual components might affect the whole instrument's performance downstream.

> "Requirements development is the most overlooked aspect of product development ... it is tempting to think that if a company builds several instruments out of the same parts, in the same way, they are in the clear."

CEOs and CTOs of start-ups are often under immense pressure from their boards and investors to get to market quickly. In particularly unfortunate circumstances, start-ups can be put under pressure to put prototypes into

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clinical trials, an idea that might sound smart to an investor who's in a hurry for a return on investment (ROI), but that doesn't account for the fact that they won't be able to change the design later without showing equivalence. Then, if the requirements aren't clearly documented, they'll have to repeat the trials, which is a huge expense.

These user-experiences are particularly crucial for drug delivery devices, which have a higher than average portion of user-experience as part of their commercial success. Well-defined requirements lead to the lowest-risk and highest ROI at launch, supported by good design and development. Principles such as human factors, ergonomics, user interface and regulatory standards all feed into a healthy requirements definition.

WHAT'S INVOLVED IN DEVELOPING REQUIREMENTS?

Requirements must be developed by compliance with standards, such as safety standards, US FDA guidance documents and more. These tasks are often referred to as the voice of the customer (VoC), user needs and usability. These activities ensure consistency and repeatability of the device and design to avoid potential problems in development, manufacture or post-commercialisation. There are major risks to skipping these steps and rushing to market, litigation and post-market failure being two of the worst scenarios. With a clear view to accepted standards, putting user feedback and user input into a design is critical in early development.

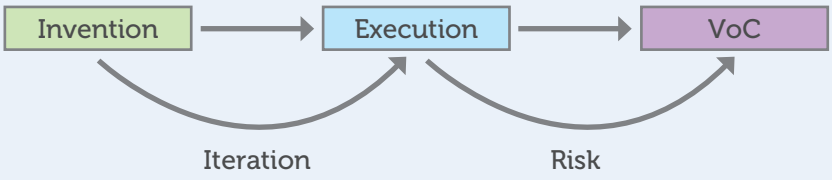
But talking to a potential patient or customer may not be the most intuitive process. In most cases, a company needs to explore the entire ecosystem, because a customer might not be immediately identifiable. For example, a company might be developing a product intended for a nurse, only to find out that if the attending physician doesn't check a specific box on paperwork, the device will never be in the nurse's hand. Understanding who will be interacting with a therapy, as well as when and how, should inform how requirements are developed.

> "Requirements must be developed by compliance to standards, such as safety standards, US FDA guidance documents and more. These tasks are often referred to the voice of the customer, user needs and usability."

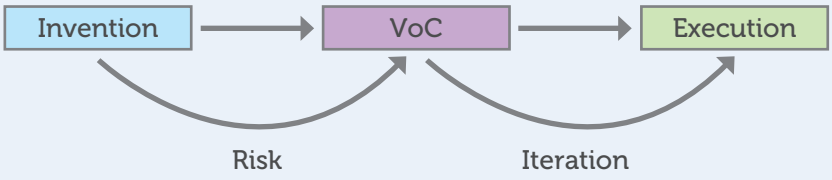
Likewise, requirements must be developed early. Waiting until later in the process, for example, in design validation at the very end of development, means risking the entire development cycle, as well as the development costs. Validating and getting user input early helps mitigate some of those potential risks, as is shown in Box 1.

BOX 1: APPROACHES TO PRODUCT DEVELOPMENT

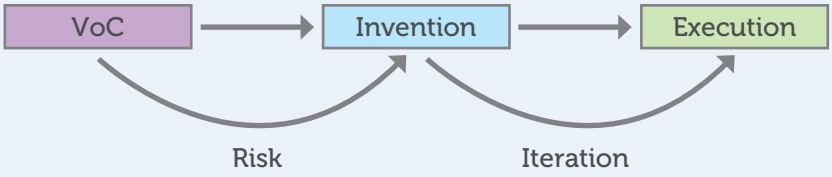
1. Early years:



2. Until recently this was the approach:



3. **Best practice**: this way you can do the least risky thing first and fail fast if necessary...



In addition, the requirements need to transfer over in every stage of development. User needs turn into design specifications, and those translate to the outputs that are verified and validated. It is important that every team member understands the underlying drive of each specification, so that they don't get lost, misinterpreted or garbled as it travels through design phases.

PAIN-MINIMISING OPTIONS FOR DEVELOPING REQUIREMENTS

Early-stage companies, and companies working to put a new product on the market, are navigating new territory. They are short of time, short on cash and are often looking for ways to skip steps. When it comes to setting solid requirements, the most effective way is to talk to every customer and ecosystem member possible. Understanding those needs and making efforts to fundamentally incorporate them into design specs will give start-ups the product development process they need.

A clear understanding of how to set requirements for a smooth regulatory path is also important. For example, "The device should dose accurately" might be an intuitive requirement to a nurse but is not sufficient to help a start-up get through regulatory hurdles. How does one measure accuracy? Is it ± 5%? In practice, the answer depends upon the product, therefore adding the specificity to what your user population expects creates a demonstrable difference. For example, "The flowmeter should meter the product accurately to ± 0.5%" is measurable and will help the company avoid repeating design cycles or ending up in field failures. You can create the specificity through literature reviews and/or competitive product analysis.

But that doesn't mean these companies are on their own. Design and development firms can play an enormously helpful role in developing functional design requirements that can help companies get to market quickly and smoothly, while managing investor expectations.

ABOUT THE COMPANY

Ximedica is a full-service product development firm that is ISO 13485 certified and FDA registered. For 30 years, Ximedica has provided a unique growth platform enabling organisations to successfully deploy medical technology products into the market. Its headquarters are in Providence (RI, US) with offices in Hong Kong, Minneapolis, San Francisco, and Silicon Valley (CA, US). In November of 2014, SV Life Sciences, a Boston-based private equity firm, acquired a majority stake in Ximedica, enabling the company to execute its growth strategy.

ABOUT THE AUTHOR

Beth Blackburn is Director of Systems Engineering at Ximedica, where she leads a broad team of engineers who ensure proper translation of user, caregiver and a variety of additional stakeholders' needs into clearly defined, verifiable design inputs. She has a BS in mechanical engineering from Worcester Polytechnic Institute (Worcester, MA, US) and an MBA from Bryant University (Smithfield, RI, US).

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Here, Quentin Ribeyre, PhD, Particle Scientist, and Filip Francqui, Managing Director, both of Granutools, and Geoffroy Lumay, PhD, Professor of Physics and Co-Founder of Granutools, and Simon Bocquet, Masters Student, at the University of Liège, Belgium, describe how three of the company's instruments can be used to characterise powder properties and behaviour, exemplified by experiments investigating the effects of adding talc to different lactose grades.

INTRODUCTION

Granular materials, fine powders and nanostructured powders are widely used in many industrial applications.[1] In particular, excipients are necessary in dry powder pharmaceutical formulations, such as dry powder inhalers (DPIs), tablets and capsules. Thus, insights regarding their behaviour and the effects of using of additives could have significant consequences for the optimisation of industrial processes, including avoiding technical issues like caking, clogging, noncompliance and non-conformity.

To increase a powder's processability, it is common to blend the excipient with an antistatic material in order to decrease the tribo-electric effect. This article will show how the addition of talc may affect lactose behaviour in terms of compaction

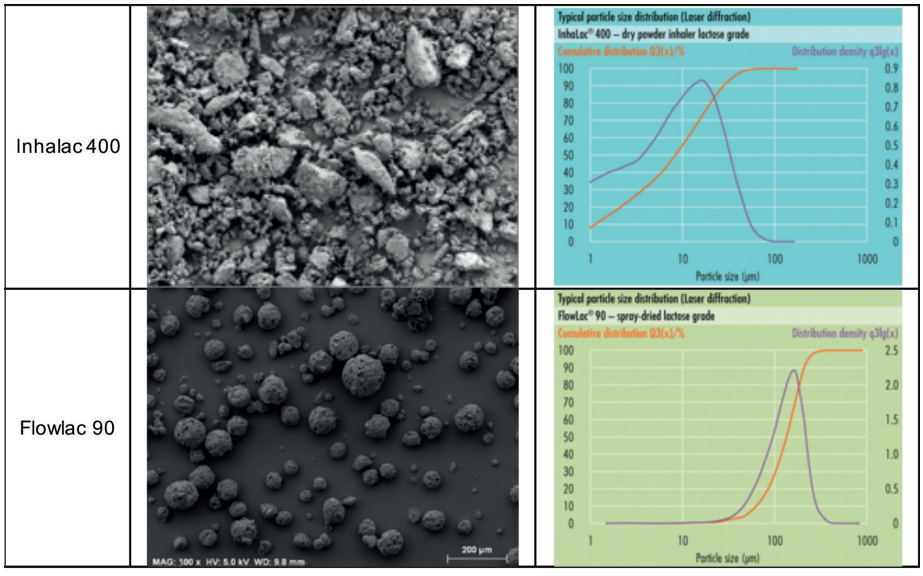

Figure 1: Photography and particle size distribution of the two lactose powders.

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dynamics, flowability, granulation and electrical charge. It will be also shown that the addition of antistatic agent addition is not always a viable solution.

MATERIAL & METHODS

Selected Powders

Two lactose products (Figure 1) provided by Meggle (Wasserburg, Germany) were used for this study:

- Inhalac 400, a high quality crystalline lactose powder, designed for DPIs.
- FlowLac, a powder produced by spray-drying a suspension of fine milled alpha-lactose monohydrate crystals in a solution of lactose.

The lactose products were placed in a chamber under ambient air conditions (42% relative humidity and 24°C) for four hours.

The influence of talc addition in these products was studied with five different mass fractions 0%, 5%, 10%, 15% and 20%. The talcum powder is a commercial powder (brand name "Care") with various ingredients, including talc, zinc oxide, magnesium stearate, perfume, Chamomilla recutita flower extract, glycerine extract and glycerine. Before the experiments, the talc was placed in an oven at 110°C for two hours.

Powder Compaction Dynamics

Powder compaction dynamics were studied with the GranuPack device, an automated instrument that uses an improved "tapped density" measurement method based on recent fundamental research.[2] It analyses the powder after it has been subjected to successive taps. Specifically, Hausner ratio (Hr), initial density (ρ_0) and final density after n taps (ρ_n) are measured precisely. Moreover, a dynamic parameter corresponding to the number of taps needed to achieve half of the compaction ($n_{½}$), and an extrapolation of the maximum density (ρ_∞), are extracted from compaction curves. Additional indexes can be used but they are not presented in this report.

The powder is placed in a metallic tube with a rigorous automated initialisation process. Afterwards, a light, hollow cylinder is placed on the top of the powder bed to keep the powder/air interface flat during the compaction process. The tube containing the powder sample is raised to a fixed height of ΔZ (generally fixed to 1 mm) and allowed to freefall.[3]

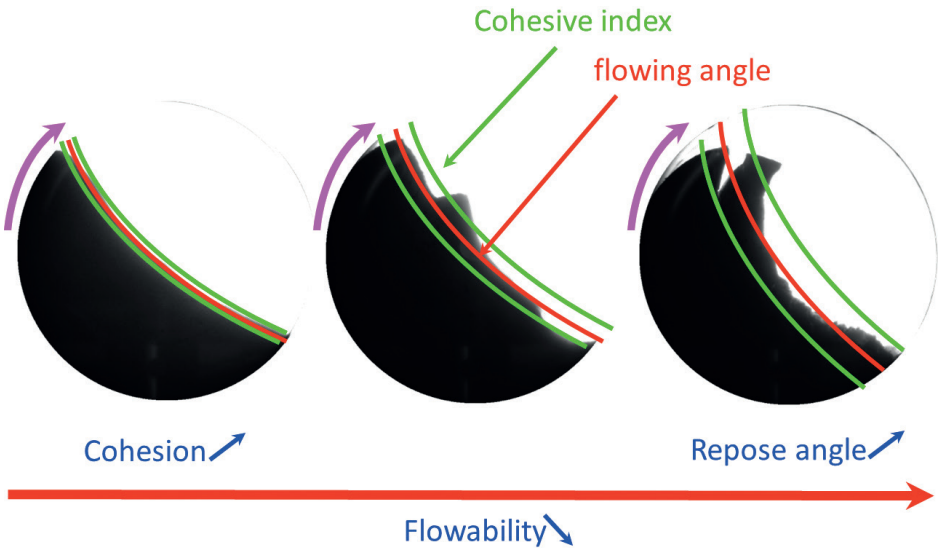

Figure 2: GranuDrum measurement principle.

Powder Flowability

Powder flowability was investigated using a GranuDrum device,[4] an automated instrument with a measurement method based on a rotating drum (Figure 2). Specifically, a horizontal drum with transparent sidewalls is half filled with a sample of powder, the drum rotates at rotational speeds ranging from 2-60 rpm, and a charge-coupled device (CCD) camera takes photographs (30-100 images per second) for each rotational speed. The air/powder interface is defined on each photograph automatically, via an edge detection algorithm. Afterwards, the average interface position and the fluctuations around this average position are computed. Then, for each rotational speed, the flowing angle (α_f), also known in the literature as "dynamic angle of repose", is computed from the average interface position and the dynamic cohesive index (σ_f) is measured from the interface fluctuations.

In general, a low α_f value corresponds with good flowability. The σf is only related to the cohesive forces between the grains. A cohesive powder leads to an intermittent flow, whereas a non-cohesive powder leads to a regular flow. Therefore, a σ_f close to zero corresponds to a non-cohesive powder. When the powder cohesiveness increases, the cohesive index increases accordingly.[5]

In addition to measuring both σ_f and α_f, GranuDrum can measure powder granulation properties with a thixotropy cohesive index (the greater this constant is for a powder, the greater its tendency agglomerate).

Electrical Charge Affinity

Electrostatic charges are created inside a powder as it flows,[6] due to the tribo-electric effect, which is a charge exchange at the contact between two solids. During the flow of a powder inside a device or vessel (e.g. a mixer, silo or conveyor) the tribo-electric effect occurs between powder particles and between the powder and the surface of the device or vessel it is in. Therefore, the characteristics of the powder and the nature of the material used to build the device are important parameters.[7]

GranuCharge (Figure 3) automatically and precisely measures the electrostatic charges created inside a powder during flow

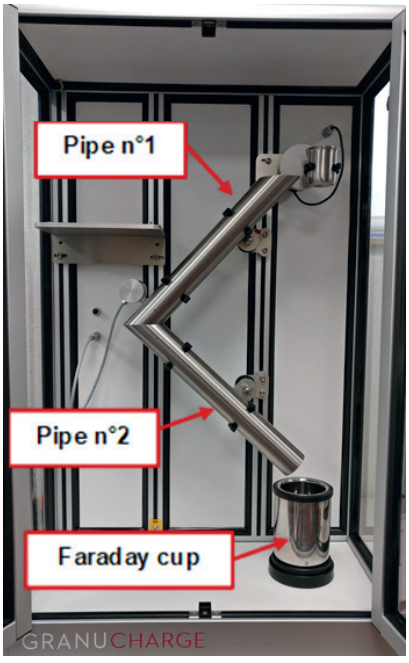

Figure 3: The GranuCharge machine.

in contact with a selected material. The powder sample flows into a vibrating V-tube and falls in a Faraday cup connected to an electrometer. The electrometer measures the charge acquired by the powder as it passed through the V-tube.

EXPERIMENTAL RESULTS

Powder Compaction Dynamics

For each experiment with the GranuPack, 500 taps (tap frequency, 1 Hz) were applied to the sample and the freefall height was 1 mm (∝ tap energy). Powder mass was recorded before each experiment and the sample was poured inside the measurement cell in accordance with the software instructions (i.e. without user dependency).

Each measurement was repeated twice and the average value and standard deviation are presented here. Figure 4 shows bulk density as a function of the number of the applied taps for each lactose blend. It can be seen that the Flowlac 90 grade is heavier than the Inhalac 400 product. Also, the greater the talc mass fraction, for the same lactose grade, the more the bulk density. This trend may be due to the size distribution of talc particle, which may be lower compared with the lactose products so that the talc particles can fill gaps between the larger lactose particles, resulting in a bulk density increase.

Moreover, the compaction dynamic results from Inhalac 400 give a sigmoid curve, whereas Flowlac 90 demonstrates linear results, meaning Flowlac 90 compacts faster than Inhalac 400. This observation is confirmed by the $n_{½}$ parameter (Figure 5), which is lower for Flowlac 90.

Another interesting observation from Figure 5 is that up to a certain limit with Flowlac 90, the greater the talc mass fraction, the faster the compaction kinetic. Thus, for this specific product, the tabletting process can become easier with a talc mass fraction close to 10%. However, above this limit, it seems that the compaction slows ($n_{½}$ increasing from 23 to 25 as talc mass fraction increases from 15% to 20%). This effect is also observed with Inhalac 400, but is far less pronounced.

Powder Flowability

For the powder flowability experiments, approximately 50 mL of each powder was analysed under standard conditions (43% RH and 25°C). Two GranuDrum velocities were investigated (1 rpm and 10 rpm) and for each rotational speed 50 pictures were taken to increase the accuracy/repeatability of measurement.

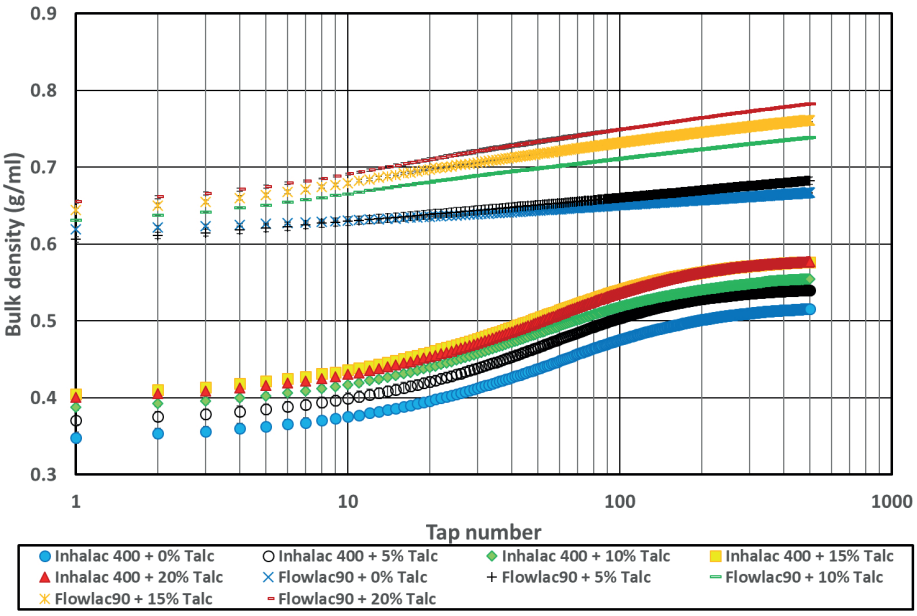

Figure 4: Bulk density as a function of number of taps for the two lactose products at different talc mass fractions.

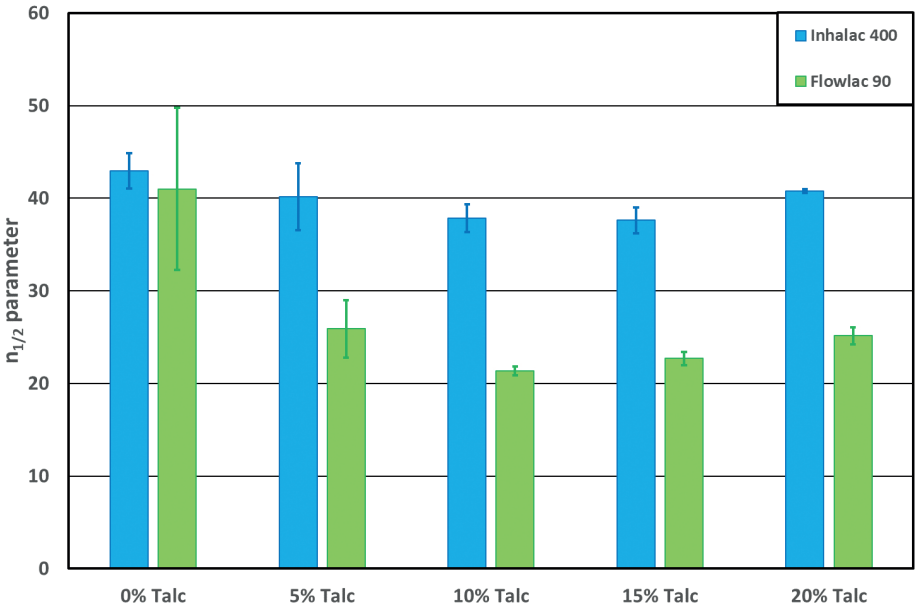

Figure 5: Measured $n_{½}$ for each lactose grade with different talc mass fractions.

Figure 6 shows the cohesive index measured at these speeds, and the thixotropy index.

With a lower cohesive index at both speeds, we can deduce that Flowlac 90 has a better flowability than Inhalac 400. However, the addition of talc increased powder cohesion (i.e. a decreased flowability) at both speeds.

Finally, judging by the thixotropy index, for Inhalac 400, the greater the talc mass fraction, the lower the tendency to agglomerate. Yet the effect is the opposite for Flowlac 90, with an increase in the talc fraction leading to an increase in the thixotropy index.

Electrical Charge

For each experiment investigating electrostatic properties of the powders using the GranuCharge instrument, stainless steel 316 L pipes and a vibrating feeder were used (see Figure 7). The quantity of powder used for each measurement was 40 mL and the powder was not reused. At the beginning of the test, the initial powder charge density (q_0) was measured by introducing powder directly into the Faraday cup. Once this step was completed, the powder was poured inside the rotating feeder, and then the experiment started. The final charge density was measured at the end of experiment (q_f).

Figure 8 summarises the results. Each charge density value corresponds to the

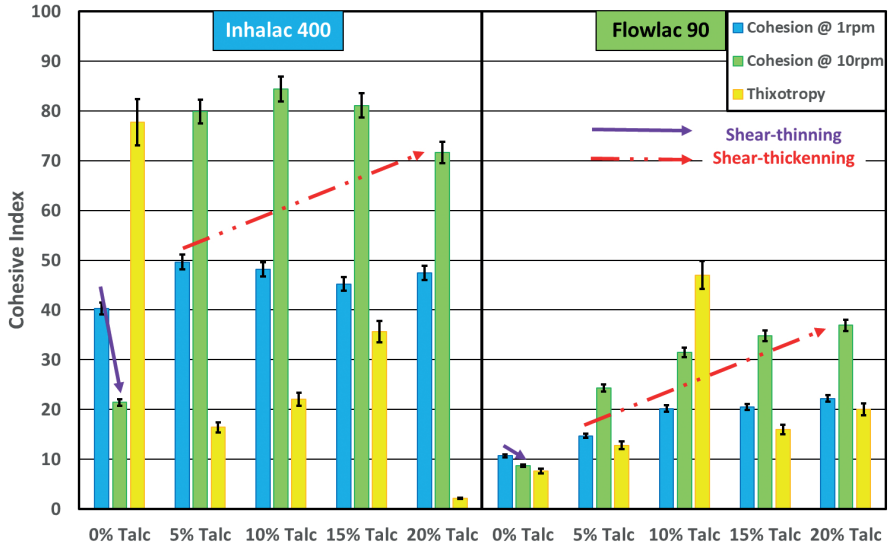

Figure 6: Cohesive index at 1 rpm and 10 rpm, and thixotropy index.

Figure 7: Vibrating/rotating feeder and stainless steel pipes.

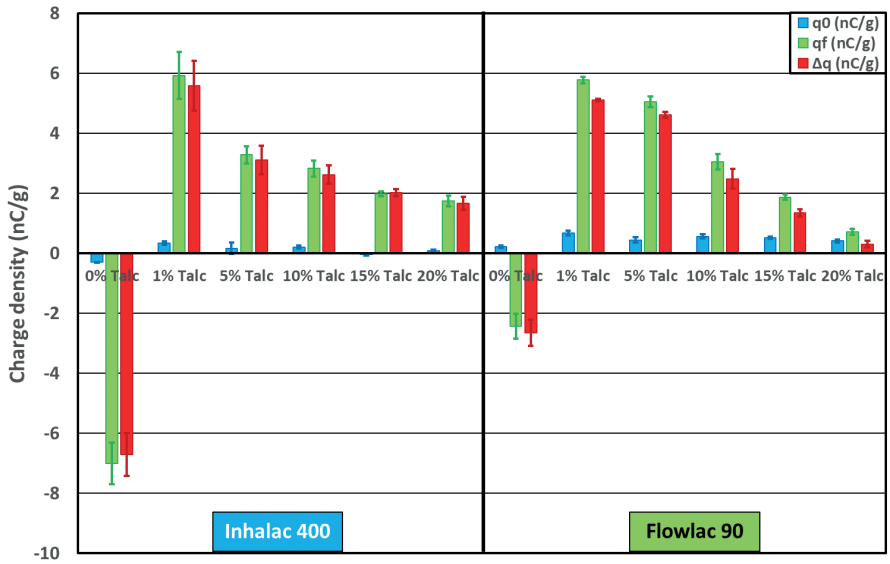

Figure 8: Comparison of initial and final charge densities for the two powders with different talc mass fractions.

average value calculated between the four tests (Δq = mean q_f - mean q_0).

The effect of talc on the electrostatic properties seems to be similar for both products. With no talc both products exhibit a negative charge density after flow in contact with stainless steel pipes, but with 1% talc mass fraction, a positive charge density can be seen. Then, the greater the talc mass fraction, the lower the electrical charge with the effect seeming more prominent with Flowlac 90. However, the highest charge densities (compared with pure powder) are observed at mass fractions below 15%. Thus, if one wants to avoid electrical charge (and consequently powder sticking on the surfaces of pipes and creating agglomerates) the addition of talc is likely not a viable solution for Flowlac 90.

CONCLUSION

We have seen how the addition of talc can affect powder behaviour and properties. It was shown that talc completely changes the powder's electrostatic properties. Moreover, we have seen that for some powders, the addition of talc is not always a means to increase powder processability. It was also highlighted that talc affects powder granulation properties and dynamic flow behaviour. Rheological behaviour may also completely change with the addition of talc, from shear-thinning to a shear-thickening behaviour. Finally, lactose compaction dynamics also changed for the blends and an improvement of compaction kinetics with the addition of talc was observed for Flowlac 90.

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THE ODTECH PLATFORM: A RANGE OF READY-TO-USE ORAL FORMS

In this article, Hugues Benevent, Senior Manager, Business Development, and Nathalie Masson, Innovation & Development Director, both of Unither Pharmaceuticals, introduce the ODtech™ platform technology for oral medications, designed to provide an easy-to-use and ready-to-industrialise solution for tackling the human factors issues of standard oral pills.

It is an under-discussed issue in drug delivery today that there is a serious problem with the traditional "Holy Grail" of the once-a-day pill oral dosage form, that being that a significant number of patients either don't like it or cannot take it. Non-compliance with oral therapies is often attributed to the medication's unpalatable taste or smell, especially in paediatrics.[1] However, studies are making it increasingly apparent that difficulty swallowing medication is also a major reason for oral therapy non-compliance.

Swallowing problems are generally underestimated. However, according to a study conducted in the Netherlands, they affect one in eight adults.[2] Another study suggests that 70% of 16-24 year-olds and 44% of those over 65 have experienced difficulties swallowing tablets.[3] Considering the ageing population, this issue must be taken seriously by pharmaceutical companies and the development of new drugs must consider this patient parameter to provide suitable formulations, particularly they must be made easier to swallow.

> "Platform technology solutions for oral formulation and industrialisation can prove invaluable when trying to address the human factors of oral therapies."

> "Swallowing problems are generally underestimated. However, according to a study conducted in the Netherlands, they affect one in eight adults."

However, the well-established manufacturing processes continue to make the standard pill an attractive dosage form for pharma, and R&D expenses and regulatory hurdles can discourage tinkering too much with the formulation once an API has been developed with demonstrable tabletability and efficacy. For these reasons, platform technology solutions for oral formulation and industrialisation can prove invaluable when trying to address the human factors of oral therapies. One such platform is Unither Pharmaceuticals' new ODtech™ range of technologies.

The ODtech™ platform produces ready-to-use dosage forms, for adapting oral medications to modern lifestyles and addressing swallowing difficulty, in a manner that is easy to adopt

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> "ODtech™ technologies produce ready-to-use dosage forms, for adapting oral medications to modern lifestyles and addressing human factors, in a manner that is easy to adopt and industrialise."

and industrialise. These technologies include:

- Proprietary particle coating technology for effective taste masking
- Proprietary particle functionalisation technology for modified and customised release of the API
- Patented formulation for ease of swallowing
- Stick-pack packaging technology, both for liquid solid forms (Unistick®).

These new solutions aim to place the patient at the centre of pharmaceutical companies' concerns, while also differentiating the medicines themselves from conventional forms, both in the over-the-counter and prescription drug market, whether for the launch of a new drug, or as a part of lifecycle management for an existing product.

In conclusion, the new ODtech™ platform, allows Unither to answer to multiple challenges. In particular, ODtech™ was developed to improve patients' lives through innovative and easy-to-use dosage forms. In addition to those mentioned here, further innovative solutions will soon be added to the ODtech™ platform.

ABOUT THE COMPANY

Unither Pharmaceuticals is a global development and manufacturing partner for proprietary and generic pharmaceutical dosage forms. It is a global leader in single unit dose technologies, such as blow-fill-seal, liquid and powder stick-packs, with a focus on affordable, portable, and easy-to-use solutions. Unither has ten facilities globally, including six manufacturing sites in France, the US and Brazil, an R&D centre in France, and a sales subsidiary in China. Unither has developed and manufactured products sold in over 100 countries and has partnered with numerous pharmaceutical companies for many years based on its history of quality performance, industrial excellence and innovation.

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ABOUT THE AUTHORS

Hugues Benevent holds a degree in Pharmacy and a master's degree in Management and Marketing. He is now works as a Senior Business Development Manager at Unither Pharmaceuticals. He has more than 20 years of experience in the pharmaceutical industry, specifically in orodispersible dosage forms business development and licensing.

Nathalie Masson holds a doctorate in Pharmacy and a master's degree in Engineering Processing. She currently works as an Innovation & Development Director at Unither Pharmaceuticals. She has more than 25 years of experience in the pharmaceutical development of solid, liquid and semi-solid oral forms, including prescription and over-the-counter pharmaceuticals, food supplements and cosmetics.

TORSTEN MASCHKE, DATWYLER SEALING SOLUTIONS

Torsten Maschke has been Chief Executive of the Sealing Solutions division of Datwyler and member of the group's Executive Board since October 2016. Before joining Datwyler Group, he was responsible for the worldwide distribution of sealing and damping solutions for the automotive industry at Freudenberg Group (Weinheim, Germany). Prior to this – having completed his education in 1996 – he was employed in various international management roles within the automotive business of the Freudenberg Group. Maschke earned degrees in Mechanical Engineering from Münster University of Applied Sciences (Münster, Germany) and Industrial Engineering from Bochum University of Applied Sciences (Bochum, Germany).

Interviewed here, Mr Maschke discusses the industrialisation of drug delivery, from the perspective of an industrialisation specialist partner for the pharmaceutical industry, looking at the trends in the field today and the advantages of the modern paradigm of partnering.

Q What would you say are the most important areas in the industrialisation of drug delivery today?

A The industrialisation of new products in the drug delivery sector is one of the most important issues that we see in the pharmaceutical industry today. What is most important within that comes down to different factors and economic developments that need to be watched closely and acted upon where fitting.

Industrialisation of drug delivery from my perspective means that products connected to drug delivery can be developed and produced on a great, industrial scale. Naturally, this is strongly linked to new developments and impulses present in the industry. One of the most important and current issues keeping the market in motion right now is the development we're seeing in the sectors of digital health and wearables, be it digital monitoring tools or drug delivery products such as wearable injectors.

The question of how those products can be industrialised is difficult to answer. From our perspective, that of an international industrial supplier, partnerships are an ideal way to join forces with experts from different fields and maximise results. In fact, we view them as "industrialisation partnerships", where synergies can be brought together, research and development can be advanced, and products can be industrialised faster, more reliably, and on a greater scale.

> "In our experience, the earlier a partnership is established, the higher the chance for success of the industrialisation. Consequently, the potential for savings also rises when industrialisation partners are involved early in the process."

In our case, we've established partnerships with acclaimed institutes, start-ups, and small companies. Their ideas, inventions, and new product developments combined with our experience in material handling, lean processes, and large-scale production are an ideal foundation to create innovative products and set new industry standards. This combined expertise and knowledge can also be of great advantage when it comes to approval processes through authorities such as the FDA or EMA.

Succinctly put, this can be described as "the best of both worlds".

Q Where do industrial suppliers come into the mix? What role do they play in the context of the industrialisation of drug delivery?

A From the perspective of an international industrial supplier with a substantial stake in the healthcare and pharmaceutical industry, we feel that the value companies like ours brings stems largely from having comprehensive experience in developing specialised components and compounds, and in-depth engineering expertise. A desirable supplier should be set up for large-scale production, a core competence for industrial suppliers.

To customers, production systems that can be applied to all facilities are incredibly valuable when it comes to developing a system and plan for the industrialisation of a new drug delivery product. The same goes for standards that are implemented globally and specify even the smallest details of the production of state-of-the-art components for drug delivery products.

In our experience, the earlier a partnership is established, the higher the chance for success of the industrialisation. Consequently, the potential for savings also rises when industrialisation partners are involved early in the process. Creating the opportunity for an exchange between partners early on is a very important cause, one that we want to promote.

Q How will patients be affected by the new developments in drug delivery industrialisation?

A Patients can ultimately only profit from the new developments in drug delivery industrialisation. New products that will help patients to administer drugs, or have drugs administered, more easily become widely and readily available once industrialisation is in place. For us, patient safety is one of our highest priorities and we feel that the industrialisation of innovative products will contribute strongly to this.

A good example is the treatment for diabetes patients. Having to administer drugs is a daily occurrence for these patients. New ways of drug delivery can facilitate this process and provide much more comfort. For example, wearable injectors and pumps can be a great relief – but these products are still new to the market and undergo continuous improvement. However, without investments in the industrialisation of these products, treatment would not be where it is today.

We are witnessing a steady growth of the global healthcare market, particularly due to better availability of treatments to a greater part of the population. Therefore, we should welcome drug delivery innovations and encourage the process of industrialisation for those with potential.

Q **In summary, industrialisation of drug delivery is very current and can be advanced through partnerships.**

A Precisely. We think industrialisation in the healthcare and pharmaceutical industry will benefit immensely from partnerships and we will certainly remain focused on the added value it can bring. Global standards and clear, lean production processes are one of the advantages industrial suppliers can bring to the table. Combined expertise and an experienced production environment will lead to better, safer and more reliable drug delivery systems for an increased number of patients.

ABOUT THE COMPANY

The Datwyler Group is an international supplier of state-of-the-art industrial components with leading positions in global and regional market segments, with a global manufacturing footprint on three continents, sales in over 100 countries and more than 7,000 employees. In its Sealing Solutions division, Datwyler provides customised sealing solutions to manufacturers and companies which operate in the healthcare and automotive industries, among others. The products and services of Datwyler are built on high-quality material, innovative technologies, outstanding engineering and process know-how.

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H&T PRESSPART

GAS PLASMA PROCESSING: A LONG-TERM SOLUTION FOR RESPIRATORY DEVICES

Ameet Sule, Head of H&T Presspart's Inhalation Product Technology Centre (IPCT), discusses the new challenges arising in metered dose inhaler design since the change from CFC to HFA propellants, in particular focusing on the tendency for drug product to adhere or degrade when in contact with the aluminium interior of the canister. As a solution, Mr Sule proposes new developments in gas plasma processing.

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Hydrofluoroalkane (HFA) propellants are widely used in modern metered dose inhalers (MDIs) due to their lack of hazardous and environmentally damaging effects on the ozone layer, compared with chlorofluorocabons (CFCs). However, an HFA formulated with an API can interact with the canister substrate, causing deposition of the drug on the canister walls or interaction with the pharmaceutical drug solution, causing drug degradation and resulting in reduced shelf life.

H&T Presspart's plasma process, manufactured under license from Portal Medical Ltd (Swaversey, UK), treats the internal surfaces of MDI canisters so that the active drug content does not adhere to the canister wall, and enhances drug stability in formulations where interactions with the aluminium substrate can lead to product degradation.

Plasma technology can also be applied to plastic parts in a dry powder inhaler (DPI), where there are challenges of cohesive powders and the surrounding conditions causing drug to be retained in the device.

> "With HFA drug suspension formulations, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels."

USE OF HFAS IN MDIS

MDIs are commonly used to treat respiratory diseases and nasal disorders. Ensuring that the device delivers a consistent dose and that the formulation is safe (non-toxic) is of paramount importance. The drugs are administered by aerosol and formulated as either a suspension or solution in a liquefied propellant gas. For over 50 years CFCs were the propellants of choice for MDIs, but these were phased out by the end of 2010 in line with the Montreal protocol, due to their contribution to ozone layer depletion.

Replacement propellants have been developed over the past two decades based on HFAs, most notably HFA134a and HFA227ea. These propellants are non-ozone depleting and chemically inert, making them the ideal candidates for medicinal products. However, some properties of

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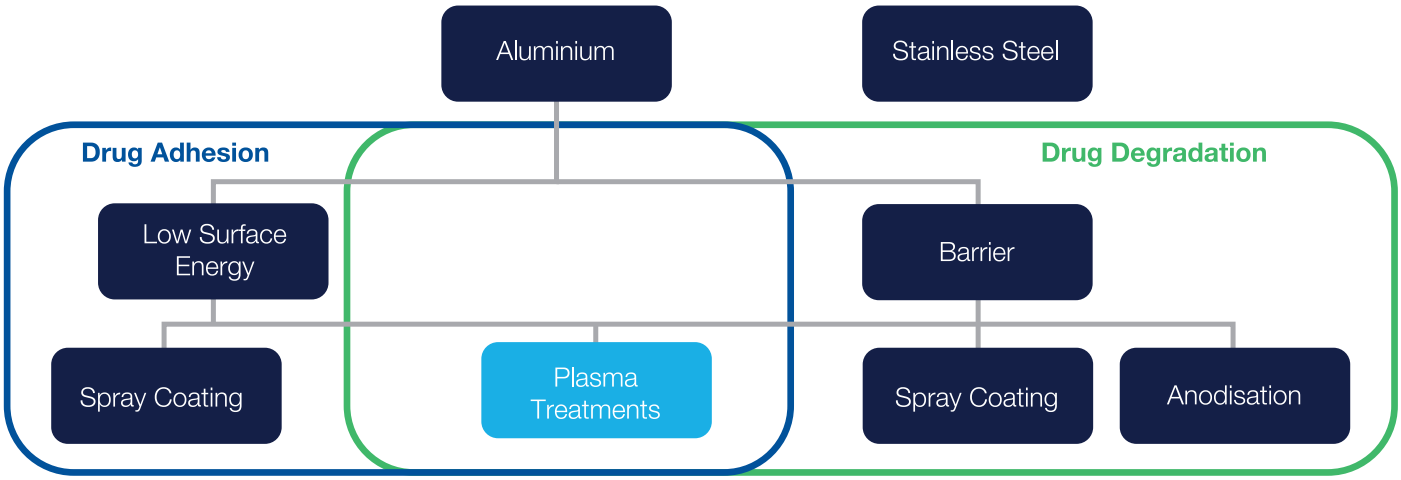

Figure 1: Types of surface treatment.

these compounds are substantially different from those of the CFCs traditionally used in MDIs, resulting in new challenges.

With HFA drug suspension formulations, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels. In both cases, the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.

The surface chemistry of the MDI canister therefore has a vital role in the overall performance of the MDI and the drug. To protect the contents from deposition and degradation, a number of surface coatings have been developed that can be applied to MDI canisters and valve components (Figure 1).

COATING MATERIALS & TECHNIQUES

Over some years a number of surface coatings have been developed to protect the drugs from deposition or degradation.

Fluorocarbon polymers (FCPs) are commonly used to coat the interior canister surfaces in order to eliminate adhesion or deposition of, for example, salbutamol on canister walls. These polymers can be made from multiples of one or more of a variety of monomers – particularly preferred coatings tend to be pure perfluoroalkoxyalkylene (PFA) or blends of polytetrafluoroethylene (PTFE) and polyethersulphone (PES), due to their relatively high ratios of fluorine to carbon. In addition, coatings that combine fluorocarbon polymers with non-fluorocarbon polymers, such as polyamides, are used for certain formulations to improve adhesion of the coating to the canister walls. Other coating types include epoxy-phenol resins.

> "Gas plasma processing can create an ultra-thin layer that protects against deposition and corrosion or modify the surface to prevent degradation."

Standard metal coating techniques can be used to pre-coat the metal substrate and cure it, prior to shaping the metal into the components, for example via deep-drawing or extrusion. This pre-coating method has the advantage of being well suited to high volume production. Other coating techniques include spraying the insides of preformed cans, dipping and electrostatic dry-powder coating, all of which can be followed by curing.

Many of these processes require high temperatures, up to 400 °C when curing, which can create additional costs and complications, and increase the environmental impact. Furthermore, only the most robust canisters (that is, those produced through deep-drawing) should be subjected to such high temperatures, as less robust canisters can become unrolled or suffer other morphological changes under these conditions.

PLASMA PROCESSING TECHNOLOGIES

More recently, plasma processes have been developed to modify the surface of an MDI canister and this approach has proved to have a number of advantages over traditional coating methods. Gas plasma processing (GPP) is an industrial technique that is carried out under vacuum to treat a wide range of substrate materials. The process involves constant or pulsed excitation of gas, either by radio frequency (RF) or microwave field, to produce an energetic plasma. The process can create an ultra-thin layer that protects against deposition and corrosion or modify the surface to prevent degradation.

It is a low-temperature process and is ideal for uniform treatments of components with complex shapes, including small components in large volumes. The coating adheres well to the component substrate, because the plasma process cleans the component surface while in the vacuum, resulting in an ultra-clean substrate-coating interface.

Using GPP to tailor the surface chemistry has the advantage of providing uniform surface treatment without changing the properties of the bulk material. The process can be used to change the outermost layers of the material only, without polymerising a coating, resulting in modifications to the functional chemistry. These modifications can be used stand-alone or with the addition of a subsequent surface coating through a single process cycle, depending on the application and desired properties.

OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI

performance, helping to reduce drug deposition and improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf life. However, the process needs to be highly controlled to ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

Plasma chemistry is critical to the performance of the coated canisters – the right choice of precursor chemistry enables a robust process with excellent performance. A variety of plasma treatments have been tried in the past, including single- and dual-layer technologies with a range of monomers, but these have failed to penetrate the market due to poor scalability and cost viability. However, alternative developments have become available that have made plasma a viable choice.

A cost-effective process has been established, using an optimised plasma chemistry consisting of an intrinsically robust monomer, highly ionised to form a high crosslink density. The ultra-pure gases and monomers do not contain any solvents, so do not produce any waste by-products. The result is a coating technology without the extractables issues potentially encountered with some polymer systems.

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister. Traditional plasma processes, be they RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in a non-uniform, thin or porous coating, which will inevitably perform poorly. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more "line-of-sight" process.

This partial "line-of-sight" process leads to non-uniformity/thickness variation in such geometries. For nanometre thin coatings on MDI cans this is observed as striations in colour or colour bands down the can. With the best compromise, the coating builds up around the canister lip, throat and base, with depletion at the rim, shoulders and can corners.

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control, designed specifically for can coating geometry, uniform coatings can be deposited.

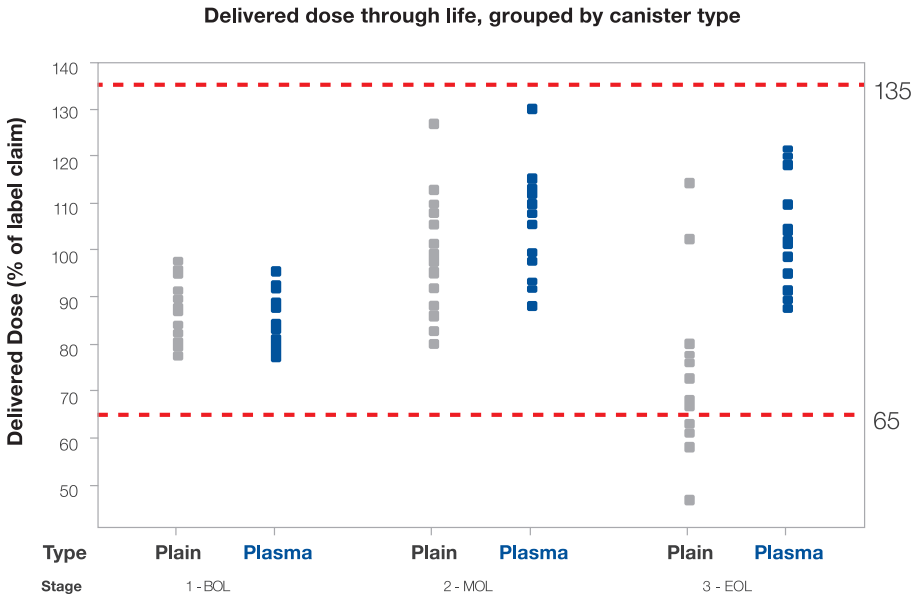

Figure 2: Comparison of delivered dose performance of a budesonide HFA suspension formulation at beginning (BOL), middle (MOL) and end of life (EOL), using plain aluminium and plasma-treated MDI canisters.

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the global MDI market.

Example: Budesonide HFA Suspension

GPP has been used to develop several different plasma coating options that have successfully prevented drug deposition on the can walls and drug degradation in solution or suspension. For example, a surface treatment has been especially developed for deep-drawn 5052 aluminium canisters, which is suitable for budesonide suspension in HFA.

As can be seen in Figures 2 and 3, plasma-treated canisters exhibited more reliable performance at the end of life. The difference in profiles observed with delivered dose and shot weight tests confirms that the primary tail-off effect relates to the concentration of drug in the formulation, as opposed to the weight of formulation emitted.

Figure 4 illustrates the conclusion that the improved end-of-life performance was achieved by reducing the amount of drug deposited on the canister walls throughout use. The canister contents were determined after depletion of formulation, with an additional 2.7 mg of residual budesonide being detected in the mean of plain canisters compared with the mean of plasma canisters.

DRY POWDER INHALERS AND PLASMA TECHNOLOGY

Another possible application of plasma technology is in the plastic component surfaces of a DPI. The various flow paths the powder needs to take through a DPI can make it difficult to achieve a consistent delivery performance. Plasma treatments are suitable for a wide range of materials, including plastics such as PTFE, polypropylene, polyethylene and polystyrene. It might therefore be beneficial to treat these parts to achieve a smoother flow and more complete evacuation of the formulation from the capsule, blister, reservoir or cartridge.

Modifying the active sites to render them more hydrophobic or more hydrophilic, dependent on the particular drug substance of interest, could enable a formulator to achieve more consistent delivery of the drug from the DPI.

CONCLUSIONS

Respiratory devices are complex in nature. Even though the MDI has been in a generic form for the last 50-plus years, it has been a challenge for R&D chemists to deliver a robust product to the market. MDIs combine a mixture of mechanical components, physical dimensions, the

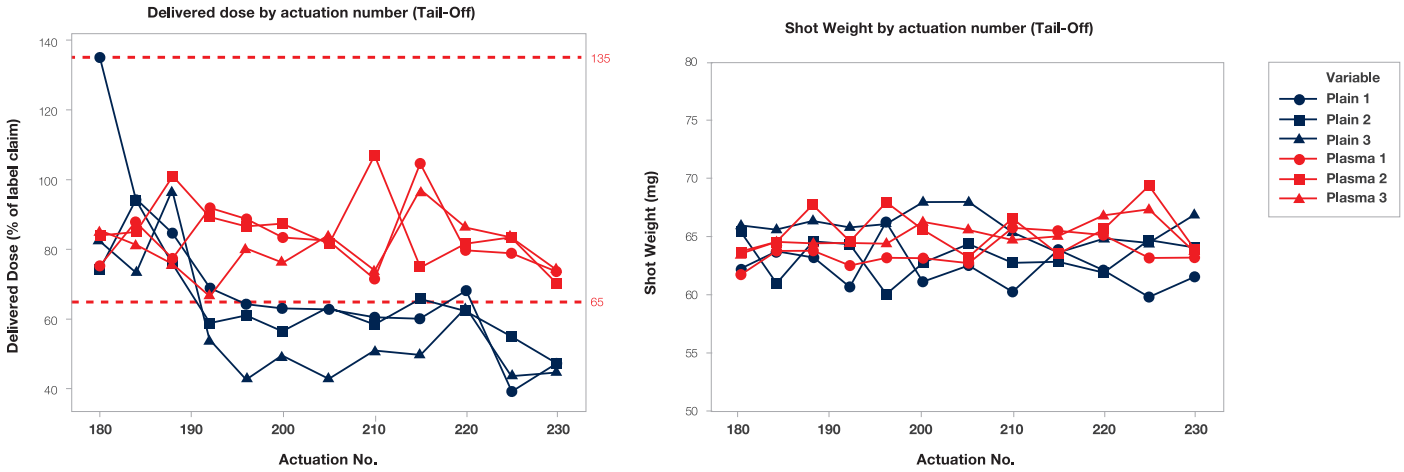

Figure 3: Tail-off characteristics for plasma-treated and plain canisters, using delivered dose testing (left) and shot weight (right), for a budesonide HFA suspension formulation.

chemical composition of the formulation and physical properties (e.g. temperature, pressure, moisture ingress), all of which affect the product characteristics.

GPP offers considerable advantages in the coating and treating of MDI canisters, improving the stability of the formulation and extending product shelf life. In addition, the ability to plasma process high volumes of the canisters fulfils the demand for high volumes from the MDI market.

Laboratory tests have already demonstrated that FCP plasma-treated canisters can provide improvements in end-of-life delivered dose performance compared with plain aluminium alloy canisters, when used in combination with a budesonide HFA suspension formulation. Other respiratory medicine applications which have been, or are being, developed include the prevention of drug degradation in solution MDIs, and the treatment of DPI components to aid the evacuation of formulation.

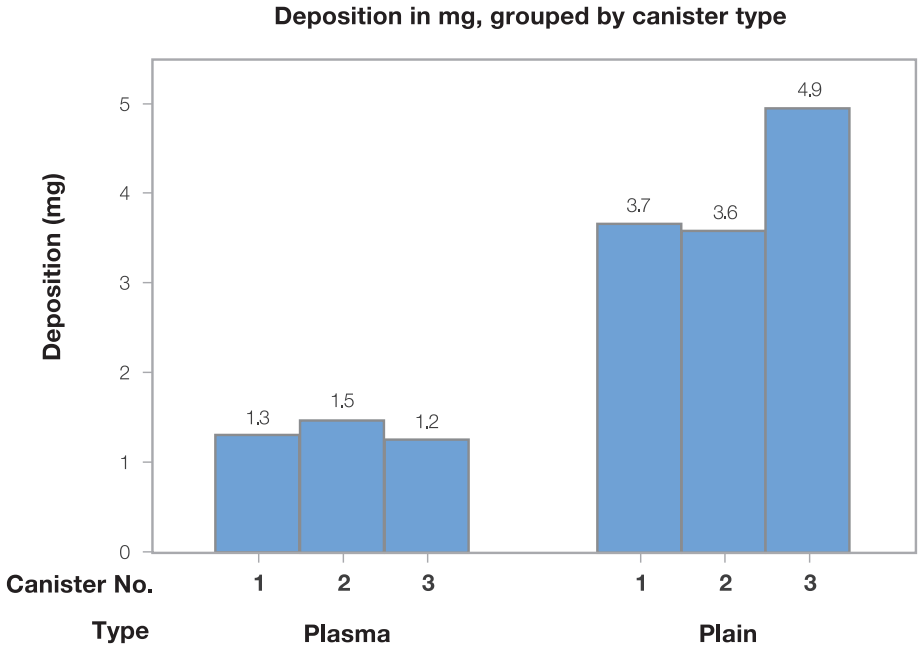

Figure 4: Drug deposition on canister walls after depletion of formulation.

ABOUT THE COMPANY

H&T Presspart offers pharmaceutical customers high-precision, injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems. The company has more than 45 years' experience and a worldwide reputation for competence, quality and innovation in the pharmaceutical and other industrial sectors. The H&T Presspart Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with sales offices in China, India, South America and the US.

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Ameet Sule, Director of H&T Presspart's Inhalation Product Technology Centre, is a pharmaceutical professional having worked in the industry for more than 20 years, specialising in the development of inhalation products and devices.

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