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:

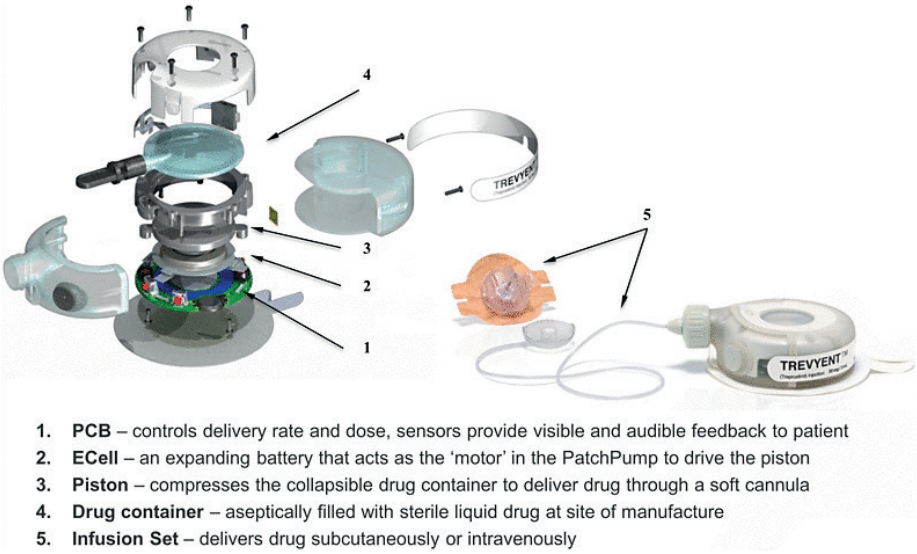
- What are the specific details of the device to ensure it functions perfectly?
- How to manufacture components?
- How to assemble components?
- How to fill the device?

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.

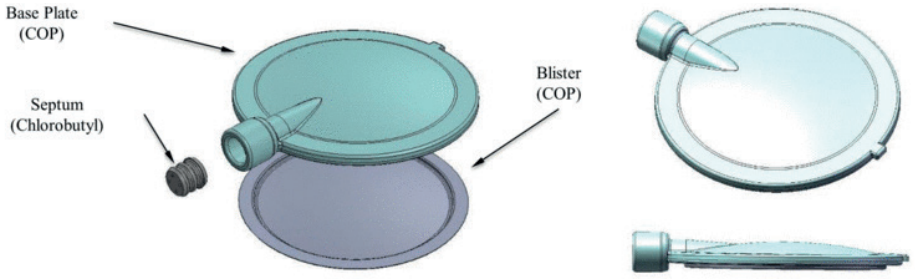


Figure 2: The primary container of SteadyMed's PatchPump.

- 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.

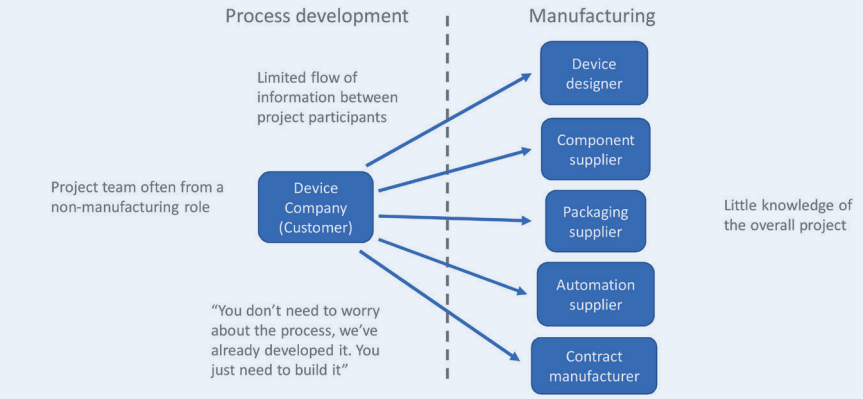
Customer Benefits

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

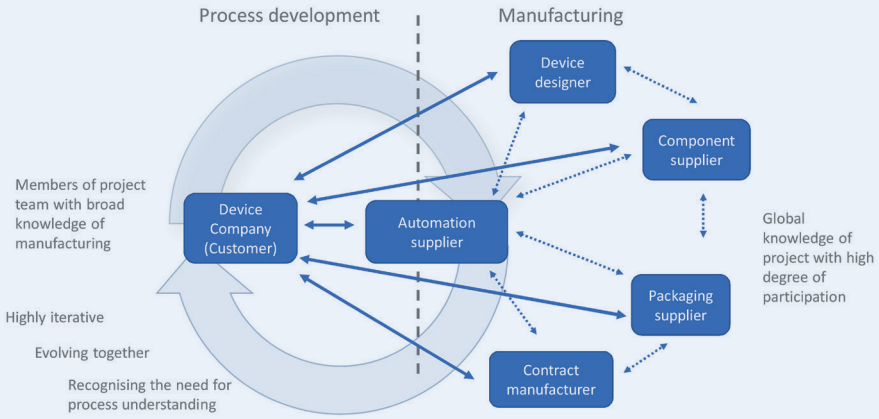


Figure 3: 3P is able to develop custom machinery for device manufacture.

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."

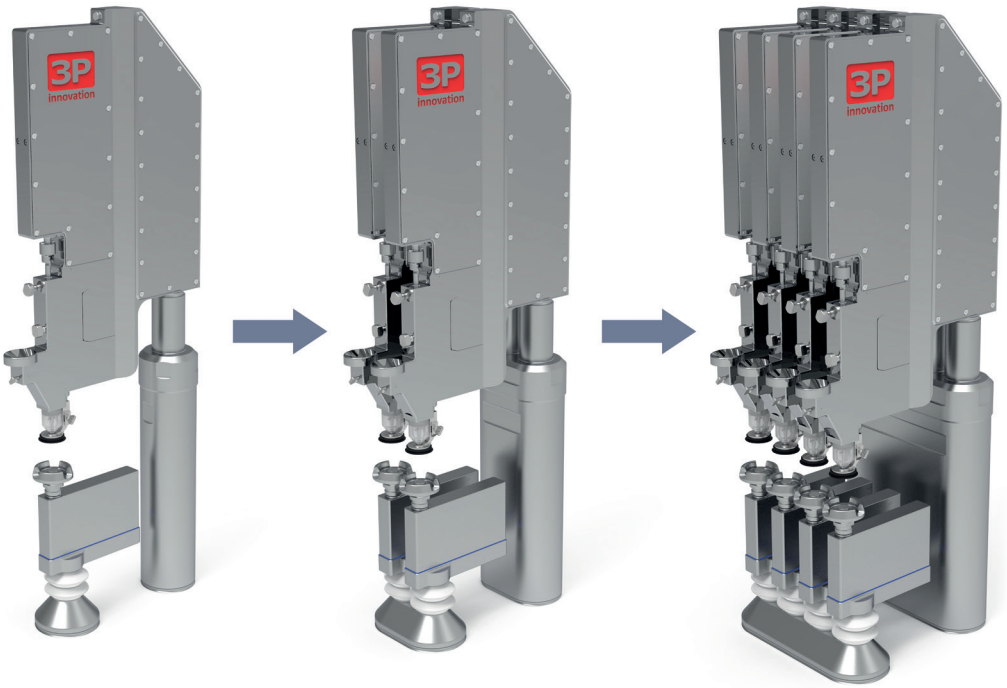


Figure 4: The Fill2Weight powder filling machine provides an example of the ability to scale by adding multiple units.

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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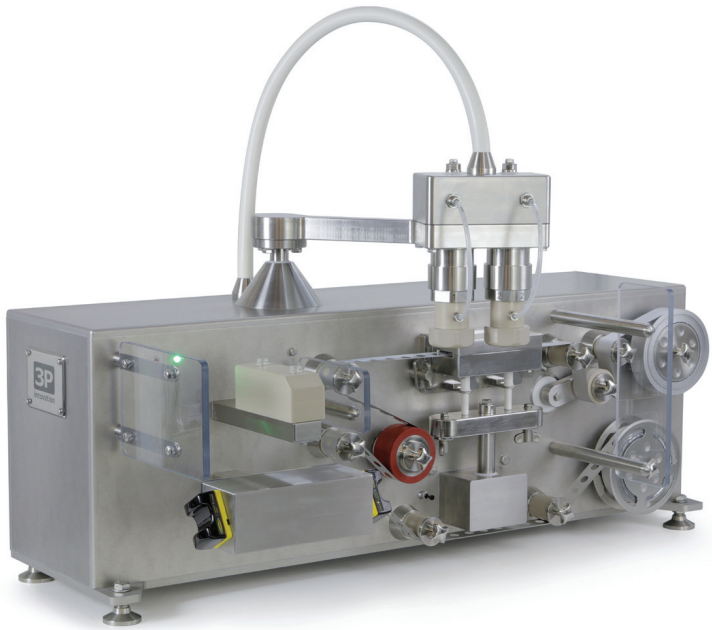

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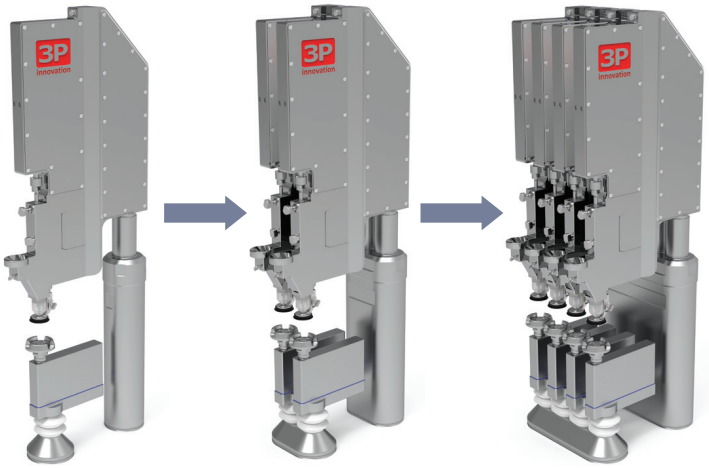

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