INDUSTRIALISATION OF INHALATION PRODUCTS: OVERCOMING HURDLES AT COMMERCIAL SCALE

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

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

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

OVERCOMING COMMON HURDLES IN COMMERCIAL-SCALE PRODUCTION

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

MANUFACTURING STRATEGY

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

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

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

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

The level of automation and associated capital investment within the manufacturing

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

Robin Heath
Commercial Manager
and Head of Supply Chain
T: +46 8 602 52 00
E: robin.heath@recipharm.com

Recipharm AB
Box 603
SE – 101 32 Stockholm
Sweden

www.recipharm.com

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

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

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

SUPPLY CHAIN MANAGEMENT

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

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

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

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

ANALYTICAL RELEASE AND STABILITY TESTING

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

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

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

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

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

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

DEVICE COMPONENT INDUSTRIALISATION AND SUPPLY

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

PROCESS TRANSFER AND SCALE-UP

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

REGULATORY CONSIDERATIONS

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

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

FINAL THOUGHT

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

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

ABOUT THE COMPANY

Recipharm is a contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. It operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US – and is continuing to grow and expand its offering for customers. Employing around 5,000 people, it is focused on supporting pharma companies with its full-service offering, taking products from early development through to commercial production. For more than 20 years, it has provided pharma expertise and managed complexity for its clients throughout the entire product lifecycle.

ABOUT THE AUTHOR

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