Considerations in selecting a contract manufacturing organization

A CMO can extend in-house capabilities during OINDP development

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Blockbuster MDI and DPI products have usually been brought to market by large pharmaceutical companies who have in-house capabilities in every aspect of product development, industrialization and supply.

As these products approach the end of the exclusivity afforded them by intellectual property rights, smaller development companies (developers) have emerged. These companies focus on gaining a share of this lucrative market, for example by developing a competing new drug delivery device or by using new approaches to formulating active ingredients, administered as either a dry powder inhaler (DPI) or pressurized metered dose inhaler (MDI).

When such companies progress toward late stage development and manufacturing of commercial quantities, there can be a need to look beyond their in-house resources to Contract Manufacturing Organizations (CMOs) with the appropriate capabilities to help them successfully manufacture their products. CMOs of various types are available, including large pharmaceutical companies.

Many considerations are involved as a developer seeks a CMO that can help them industrialize, manufacture, supply and provide technical support throughout the product's life cycle. These factors include:

- Manufacturing strategy
- Equipment specification and procurement
- Analytical testing
- Device component manufacturing and supply
- Process transfer and scale-up
- Regulatory considerations
- Supply chain management and product maintenance

This introductory article discusses some of these considerations for MDI and DPI contract manufacturing.

Manufacturing Strategy

Developing a sound manufacturing strategy may be the greatest contribution a CMO can make. Understanding the factors that influence finished product

batch size and manufacturing throughput is a fundamental aspect of determining capacity and unit price. The aim is striking an optimum balance between commercial batch scale, level of capital investment, resulting capacity and unit cost of the finished product.

For example, in DPI products, batch size is often governed by blend scale. However, other considerations may be capacity of the filling and assembly equipment or its impact on the blend and finished product performance, for instance, due to powder compaction or segregation. Conditioning may be required, for instance a hold time for either the blend or filled product. End-to-end manufacturing often needs to be separated into discrete stages, allowing confirmatory testing to occur before adding further value to the product. These requirements need to be factored into the logistics of the manufacturing process and facility design.

Given the relatively universal design of MDIs, it may not be necessary to commission a manufacturing operation around a bespoke product. Instead, existing equipment, such as the MDI filling line (shown below) may be used and the commercial batch size dictated within a CMO's installed capacity.

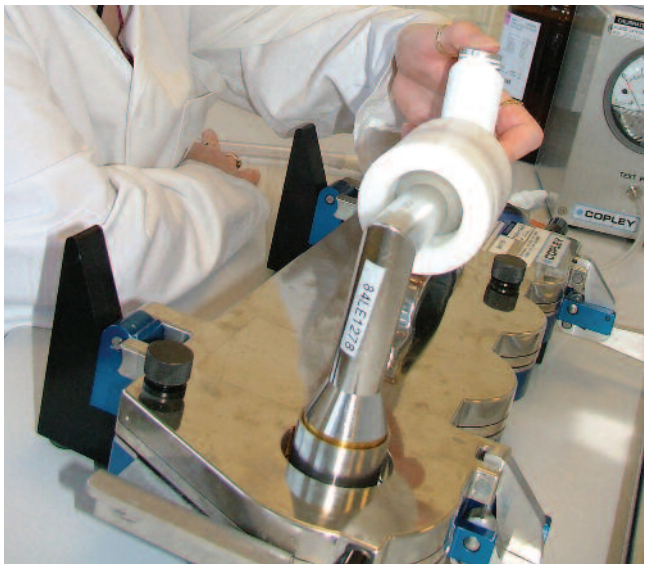
An MDI filling line

Equipment specification and procurement

Manufacturing strategy will also be impacted by the level of automation and associated capital investment in the process. This may involve a compromise between the relatively high initial investments associated with full automation versus a lower capital but higher ongoing labor cost solution. A developer should be confident about a CMO's ability to provide cost and timescale certainty, as well as their ability to specify equipment, facility modifications and work methods to satisfy cGMP requirements and HSE needs, including containment and emissions. Some CMOs may also be positioned to provide improved purchasing leverage, thereby reducing overall investment costs.

Analytical testing

Analytical method transfer from the developer to a CMO can be especially challenging when industrializing and manufacturing inhalation products. It is essential to deliver robust methods that are both precise and accurate, and which ensure the product conforms to exacting regulatory standards. This is especially true for delivered dose and aerodynamic particle size distribution. In addition to selection and control of starting materials and the manufacturing process, key factors may include environmental control within a CMO's laboratory, method automation and equipment. For example, a Next Generation Impactor (NGI) (shown below) may be used to deliver improved precision. In some cases, variability within an analytical method may be found unacceptable. In these circumstances, analytical method development expertise within a CMO well versed in six sigma improvement techniques can be valuable.



A Next Generation Impactor (NGI)

Stability study management may also present challenges, due to tight product specifications and the implications for testing resources, which can be intense and variable. Selecting a CMO well versed in testing inhalation products, including the testing of excipients and physical characterization of active ingredients, could also provide distinct advantages for the developer.

Device component manufacturing and supply

The delivery devices used for MDIs and DPIs are integral parts of the product. This presents an additional

level of complexity due to the need to industrialize the components in addition to developing the manufacturing process. This is especially true for DPIs where the developer often acts as the design authority, possessing in-depth knowledge of the device design and function. A CMO experienced in mould tool scale-up and device assembly manufacturing can present an opportunity to build on the understanding the developer may have gained from single or low cavity injection mould tools and manual or semi-automated assembly processes. This can help ensure reliable component supplies at industrial volumes.

When the developer's product is an MDI, consideration should be given to selecting a CMO with a thorough knowledge of valve and canister components, as well as moulded device actuators. This may enable a CMO to provide insight regarding industrial scale manufacture, such as compatibility with automated packing processes where actuator cap fit and dose counter security can be concerns.

Process transfer and scale-up

While development of a robust product is the responsibility of the developer, a CMO should possess the expertise to understand sources of variability within manufacturing and analytical processes that could influence critical product parameters such as assay, particle size distribution and dose. Application of a six sigma statistical approach by a CMO can help a developer maximize the effectiveness of their scale-up/transfer program, ensuring final product specifications take into account major sources of variability. Examples would be manufacturing an appropriate number of batches and utilizing multiple lots of input materials and components. The resulting benefits can translate into improved outcomes during validation and reduced batch failures during routine supply.

Regulatory considerations

First time regulatory approval is the goal of any organization looking to commercialize and launch a new product as delays represent significant lost revenue. Choosing a CMO experienced in writing successful regulatory dossiers can provide valuable input and guidance for the developers regulatory package. Some CMOs may be able to extend this to full CMC (chemistry, manufacturing and controls) dossier preparation service if required.

When selecting a CMO, a developer should also carefully consider the compliance pedigree of the proposed facility and its ability to achieve successful inspection results without experiencing delays from unfavorable observations.

Supply chain management and product maintenance

An important aspect of manufacturing any new pharmaceutical product is establishing and managing a reliable supply chain. From raw material procurement to finished product distribution, the entire supply chain needs to be understood in order to ensure risks are identified and effectively mitigated. If these competencies do not reside in a developer's organization, they may wish to select a CMO that can assist in establishing the supply chain. A CMO might also operate the supply chain, utilizing technical, quality and commercial personnel to optimize the quality and cost of raw materials and device component supplies. Depending on size and buying leverage, a CMO may be able to obtain financial savings on behalf of the developer.

Inhalation products are relatively complex and inevitably, even with careful supply chain management, there may be situations when a supplier needs to modify or substitute materials. For example, this type of product maintenance activity is needed where consolidation within the polymer industry continues to result in the rationalization of polymer grades. In such cases, a CMO with a thorough understanding of regulatory requirements, complemented by the technical ability to qualify new materials, can be a useful partner for a developer.

A key decision

Selection of a CMO is a critical decision for a developer seeking contract manufacturing services. Making that decision is even more important when the product is relatively complex, as is the case with inhalation products. Careful evaluation and selection of a CMO can allow a developer access to a broad range of technical and commercial expertise to suit the needs of their particular new product development. This not only helps ensure their product is reliably manufactured and supplied, but also gives them the capabilities to respond to the inevitable technical challenges that arise during a product's life cycle.

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