Kindeva
DRUG DELIVERY

COLD FILLING VERSUS PRESSURE FILLING: THE CASE FOR VERSATILE, FULLY INTEGRATED CDMOs

In this article, Steve Haswell, Process Development and Tech Transfer Team Leader at Kindeva Drug Delivery, compares the two main processes for manufacturing pressurised metered dose inhalers – and examines the value for pharmaceutical companies of working with contract development and manufacturing organisations that have expertise in both processes.

Kindeva Drug Delivery traces its legacy back to the development of the world's first pressurised metered dose inhalers (pMDIs) in 1956. In more recent decades, the inhalation industry has seen diversification of device formats ranging from the proliferation of dry powder and soft mist inhalers to the introduction of connected inhalers. While there is much discussion on the relative advantages and disadvantages of different device types, the pMDI continues to be a critically important device.

Although pMDIs can appear to be similar from a patient's perspective – with use and technique being largely the same from one pMDI product to another – there are important differences among pMDI products. Formulations for pMDI products can vary quite significantly, with different chemical and physical properties. This variation affects not only how these drug products are formulated but also how they are manufactured.

There are two predominant processes for manufacturing pMDIs: cold filling and pressure filling. This article provides a comparison between these two processes. It also examines the value – from the perspective of a pharmaceutical company – of working with contract development and manufacturing organisations (CDMOs) that possess capabilities and expertise in both processes. This article also reflects on the introduction of quality-by-design (QbD) initiatives and emphasises the importance of CDMOs with integrated, end-to-end capabilities and expansive cross-functional expertise.

pMDI MANUFACTURING OVERVIEW

At a high level, the pMDI manufacturing process can be segmented into five stages: propellant batching, concentrate preparation, canister filling, post filling and equipment cleaning (Figure 1).[1]

Because standard pMDI propellants are gaseous at ambient temperature and pressure, they must be liquefied before manufacturing equipment can process them and effectively fill the pMDI canisters. In the propellant batching phase, the propellants are liquefied by either lowering the temperature within a refrigerated vessel (used in a cold-filling

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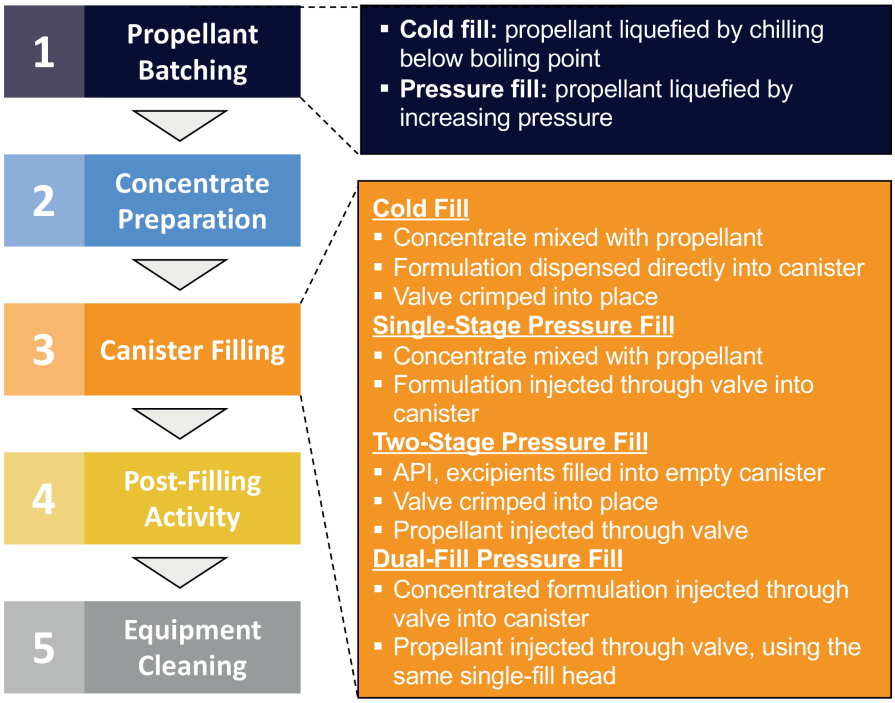

Figure 1: Overview of the pMDI manufacturing process.

process) or by increasing the pressure in a pressurised vessel (used in a pressure-filling process). Then, during the concentrate preparation stage, the API is combined with a liquid solvent or a propellant and then transferred to the batching vessel.

Canister filling differs by cold-fill and pressure-fill processes and may be conducted in a single stage or in two stages. In cold-fill processes, the API or concentrate is pre-mixed with the propellant at a low temperature and then dispensed into empty pMDI canisters. A metering valve is then crimped into place. Importantly, formulation is not driven through the valve.

In a single-stage pressure-fill process, the metering valve is pre-crimped onto the canister before filling. The formulation – API or concentrate pre-mixed with the propellant under pressure – is injected through the valve, into the canister. In a two-stage pressure-filling process, the concentrate is first dispensed into an empty canister, the metering valve is crimped into place and then the propellant is injected through the valve.

More recently, in addition to the single- and two-stage processes, a dual-filling process has become available. Under this process, a concentrated formulation is dispensed through a pre-crimped valve, followed by the propellant using a single fill head. An advantage of the dual-filling technique is that the addition of trailing propellant through the valve helps to cleanse the API residue from the internal pathway within each valve. This process is gaining popularity as the related process patents expire.

Post-filling activities involve a series of in-process controls to challenge and test factors such as fill weight, crimp dimension, heat stress and function. Through-batch units can be sampled for product release testing. Finally, the equipment must be cleaned. Cleaning methods are developed, optimised and validated for each pMDI programme and consider a variety of factors, including the equipment design and the toxicity of all the APIs, excipients and cleaning materials used on that equipment.

CONSIDERATIONS FOR COLD FILLING AND PRESSURE FILLING

In the current landscape of drug development, in which pharmaceutical companies are investing in dual and triple combination products that contain multiple APIs, the selection of pMDI manufacturing process is crucial.

Pressure-filling techniques are best suited for solutions where the API is fully soluble in the final formulation.[2] On the other hand, pressure filling can present challenges for suspensions where the API is not soluble. The challenge for pressure filling is particularly true with suspensions that have high powder loads. Pressure filling these formulations can create clogging of the valve and fill head as a result of the highly concentrated API.

The dominant pMDI manufacturing process in the industry is the single-stage pressure-fill process. The prevalence of pressure filling is at least partially attributable to its operational accessibility. Despite some operational advantages, there are a myriad of factors that must be considered when selecting between cold- and pressure-filling processes (Table 1). Both have advantages and disadvantages.

	Cold Fill	Pressure Fill
Filling Speed per Unit	• Bespoke • Low number of fill heads	• Multi-head, off-the-shelf equipment available
Formulation Type	• Solutions or complex, high powder loaded suspensions • Cold tolerant	• Solutions to medium powder loaded suspensions • Stability in vessel • Accurate propellant top-up through batch
Valve Selection	• Fill into open can	• Fill through valve
Process Equipment	• Materials of construction (MOC) that will tolerate low temperatures	• MOC that will tolerate high pressure and provide effective sealing
Fill Weight Accuracy	• Important for accuracy of number of shots	• Same as cold fill in single-stage process • Critical in two-stage process as final drug content is impacted
Unit Purge Requirements	• None	• Unit must be purged or vacuum crimped
Valve Equilibration & Gasket Swelling	• Begins later in process during spray testing	• Begins at start of filling process

Table 1: Considerations, advantages and disadvantages for filling processes.

Pressure filling may become more challenging for dual and triple combination products as they can have higher powder loading. To successfully pressure fill such formulations, manufacturers will need to select a valve that can withstand higher powder densities. Even with careful valve selection, the valves can be susceptible to clogging. Cold filling is not challenged in the same way, since the formulation is not injected through the valve during filling.

While cold filling tends to be a more appropriate process for high powder load suspensions, it is not without its challenges. First, formulations must be tolerant to cold temperatures, since cold filling is performed at temperatures between -60°C and -50°C. If a formulation is at the edge of solubility, it may not be a good fit for cold filling, as the API may come out of the solution at low temperatures. Moreover, cold-filling equipment and pMDI components can be susceptible to water condensation or ice formation, which can result in moisture uptake.[2] To avoid this, cold filling requires strict environmental controls.

THE IMPORTANCE OF CDMO VERSATILITY

Based on these considerations, there is no single manufacturing process that is categorically best in every situation. Rather, the scientific literature urges that the selection of a manufacturing process should be a product-specific approach.[2] This selection should not be strictly determined by the options that the manufacturer has available. Therefore, CDMOs with the equipment, capability and experience to provide both pressure filling and cold filling can offer an optimal approach and important advantage to their pharmaceutical partners.

When Kindeva formulators begin working with a partner on the development of a new inhaled product, manufacturing considerations are discussed from the very first phases of the programme. As part of the feasibility stage, the Kindeva technical team evaluates both the pressure-filling and the cold-filling options. Kindeva scientists are able to deduce the optimal filling process early on. It is important to consider both processes in the feasibility stage. Since the suitability of the filling process is dependent on the product and the formulation, Kindeva's ability to evaluate the suitability of both pressure-fill and cold-fill processes during the early feasibility stage, as well as the ability to scale the process to commercial production, enables alignment of the manufacturing process to the specificities of the client's product.

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The optimal selection of a manufacturing process at the feasibility and development stages is extremely significant for pharmaceutical companies because of the potential impact this decision has on long-term product performance and quality. The choice of filling process can impact critical product quality attributes such as aerodynamic particle size distribution (APSD), delivered dose uniformity (DDU), canister content assay, fill weight and moisture.[2] For example, with suspension formulations, a precise level of particle disaggregation is needed to attain the required APSD consistently.

Additionally, regardless of which manufacturing process is selected, the volumes of concentrate and propellant must be carefully controlled, which traditionally has been more challenging in two-stage filling processes. These types of quality issues can ultimately impact the performance of the product at the patient level. Therefore, a CDMO that has the versatility to deploy a variety of manufacturing processes is in a better position to help reduce the risk of future quality issues that arise for their pharmaceutical partners.

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THE VALUE OF END-TO-END CAPABILITIES

Recent QbD initiatives, along with industry best practices, stipulate that quality must be designed into the product, requiring an understanding of the relationship between raw materials, formulation, process development and, ultimately, the performance of the product.[3] In order to design a successful manufacturing process, it is beneficial to have cross-functional expertise, rather than specialised expertise in a single functional area. At Kindeva, every aspect of the business is engaged at the onset of the programme, with collaboration among global experts in formulation, analysis, device development, clinical trials, quality, manufacturing, regulation and marketing. This level of engagement is not only necessary to design an appropriate manufacturing process, it is valuable for designing a winning commercial strategy and high-performance product.

It is important not to overlook the product's commercial strategy when selecting a manufacturing process. Two-stage filling processes are often difficult to scale up, have lower output rates and can present difficulties in repeatedly dispensing concentrate accurately – and therefore may be less preferable in large-batch situations.[2] Moreover, it is valuable to work with CDMOs that have manufacturing capabilities and experience at a commercial level, not just at the bench scale. Some process risks may not be relevant at the bench or pilot scales but can manifest during scale-up and commercial manufacturing processes.[2] These risks can be mitigated by evaluating process development with a commercial lens at the programme's inception.

Choosing a CDMO with a strong regulatory and clinical track record can be especially valuable. For customers that have identified the countries in which they want to market their product, it is important to involve the clinical and regulatory team as early as possible, so that they can provide valuable counsel as the programme develops. Early involvement of the regulatory experts supports the robustness of the regulatory strategy at the time of submission. Kindeva can provide this regulatory and clinical expertise based on its track record of product development,

scale-up and regulatory approval of both inhaled and transdermal products.

CONCLUSION

Of the two dominant manufacturing processes for filling pMDIs – cold filling and pressure filling – neither is categorically superior. Rather, each strategy has benefits and the filling process should be selected primarily based on the physical properties of the individual formulation. Therefore, CDMOs should evaluate the suitability of both filling processes for their partners' products. The evaluation and selection process exemplifies the value of choosing a CDMO that has the capability and experience to develop multiple types of manufacturing processes.

The selection of a pMDI manufacturing process – from feasibility through to commercial supply – further illustrates the value of possessing end-to-end, cross-functional capabilities. Kindeva engages every aspect of the business at every stage of development. This multifaceted expertise is leveraged to design a high-performance product and develop a manufacturing process and regulatory strategy that will achieve the pharmaceutical partner's commercial objectives and secure long-term supply of reliable products to patients in multiple markets.

ABOUT THE COMPANY

Kindeva Drug Delivery is a CDMO offering its partners integrated, end-to-end capabilities spanning formulation, product development, scale-up manufacturing and commercial manufacturing. Its full-service innovation offering covers: inhalation (pMDIs, dry powder inhalers, connectivity and nasal delivery); transdermal delivery (drug-in-adhesive systems and gel patches); and intradermal delivery (microneedles based on solid and hollow microstructures). Kindeva Drug Delivery has locations in the US and the UK and employs approximately 1,000 people. The company has a long track record of industry firsts, including the first pMDI, the first drug-in-adhesive patch, the first breath-actuated inhaler and the first CFC-free pMDI and CFC-free nasal pMDI.

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