From Feasibility to Final Product: Delivering Success for an Inhaled Development Program

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There are many factors that need to be considered and evaluated when it comes to selecting the most appropriate delivery platform for an inhaled product. No two drug programs are likely to have exactly the same drivers, so these factors need to be evaluated afresh for each new product concept and development program. It is therefore important to approach defining the target delivery technology in a "device agnostic" manner, and to not necessarily be swayed by previous programs or a technology bias towards a single platform – be it a pressurized metered-dose inhaler (pMDI), dry powder inhaler (DPI), or nebulizer.

So what are the considerations that need to be taken into account? There are technical considerations such as the physical properties of the active pharmaceutical ingredient (API), for example, whether it is readily solubilized or not; whether it is a small molecule API or a biologic; and what the likely dose range will be. There are also patient considerations, such as the age range of patients and whether they may have any dexterity or cognitive issues which could influence device usability and compliance with dosing, what the patient's lifestyle is, and what expectations they may have based on other available devices. Additionally, there are time and cost considerations including the cost and availability of the API, especially at early stages of development, as well as the cost of any device and likely volumes; while strategic issues include the development strategy being employed, and the nature of the client or development partner and their need for early value inflexion on clinical proof-of-concept.

From a commercial standpoint, other important factors to consider include whether the product is a generic or an innovator product, as well as the project's goal (commercialization or out-licensing to a commercial partner), and if final product manufacture will be carried out in-house or will be outsourced.

Finally, the disease needs to be taken into account, and whether the therapy will be delivered at home or in hospital, whether delivery needs to be to the deep lung or the central airways, the number of doses per day, and the suitability of the product for treating the disease in question. Platform technology objectives may vary through the development process based on the potential for making the development process more complex – a single platform choice may not necessarily be appropriate for the duration of a program. Making informed choices at a given stage of development can save time and money and can maximize the probability of a project's success.

The choice of delivery platform for an inhaled development program may be driven by different factors at different points in the development cycle. This means that, although keeping with the same platform throughout may be preferred, for some programs there is the opportunity to change the delivery platform from the one used in the earlier stages of development, even up to proof-of-concept, to the one that ultimately might be commercialized.

Case Study 1: How Nebulization Can Move a Product Quickly and Cost Effectively into the Clinic

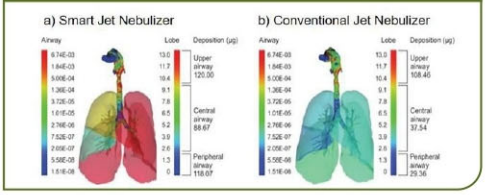
When working with a new chemical entity (NCE) that has a very uncertain future, focusing on only one delivery platform, that will be used throughout all stages of development, can be expensive, so it is beneficial to work in the fastest and most cost-effective manner at the early stages, knowing the final commercial product may not use the same platform as in the early stages of development. Success in proof-of-concept studies is most important at this phase, so dosing flexibility, as well as speed and careful cost management are the key driving forces.

A small molecule development program for a niche disease and a number of enabling factors contributed to an innovator company deciding that the molecule was best delivered via smart nebulization. The molecule was very water-soluble and was in the higher dose range making it potentially less amenable to being formulated as a DPI, although a capsule format might also have been suitable.

For the disease indication in question, it was beneficial to target very high and deep lung deposition to maximize the probability of success (PoS). A hand-held mesh nebulizer for this development program was chosen as it allowed all of the preclinical pharmaceutical development work to be completed with only a small quantity of material (100 g). This was sufficient to conduct all of the formulation development work and analytical method development as well as phase-appropriate validation, stability testing and product performance characterization studies, these latter studies being for a high dose (10 mg). A further advantage of using the chosen platform was the ability to deliver a variety of different clinical doses via only two solution strengths by dispensing different volumes into the nebulizer. The project resulted in a clinic-ready product in only 18 months.

Figure 1 shows *in-silico* lung deposition modelling work carried out with a smart jet nebulizer versus a conventional jet nebulizer for a suspension product. The figure shows, via a 'heat map', how much higher the lung deposition was for the smart jet nebulizer, with twice as much drug being deposited in the central airways versus the conventional system, and almost four times as much in the smaller airways.

Figure 1. *In-silico* lung deposition modeling for a smart jet nebulizer versus a conventional jet nebulizer



In this *in-silico* lung deposition study, smart nebulizers have been shown to be superior to conventional nebulizers in terms of lung deposition, and also significantly higher than for a high-performing DPI. This difference may be important in the quest to maximize the probability of success in the early stages of development, as the more drug that can be dosed to the lungs and the more reproducibly that is achieved, the better the chances of a positive outcome.

Other advantages of a smart nebulizer approach include the potential for more consistent delivery because the patient is guided to take every breath by the device. In the mesh nebulizer system in the case study the dose sits on top of the mesh and typically more than 90 percent of the dose is delivered to the patient. In addition, this approach is generally conservative in its use of material because there is only the need to dissolve up as much drug as is required for the immediate testing that needs to be carried out, meaning that expensive or scarce API is not wasted during development.

Smart nebulization can be a very effective way of developing a product to the early clinical stage and quickly maximizing lung deposition consistently from patient to patient with a simple and straightforward formulation development process, consuming minimal material to get the best probability of success.

Case Study 2: DPI Product Development and Scale Up

Any choice of delivery platform must be fit-for-purpose both from a design and manufacturing perspective and also from a patient-use perspective. As with all development projects, it is beneficial to minimize material requirements and costs and look to mitigate risks associated with the scale-up of the manufacturing process.

One of the dilemmas of drug product development, particularly in the respiratory field, where reliable scale-up can be difficult to achieve, is deciding what constitutes an appropriate scale at each stage of development. Thus, in early development, when materials are often in limited supply, there is an inevitable trade-off between scale of manufacture and the number of batches that can be produced in order to build scientific understanding. Whilst manufacture at the intended commercial scale is most representative, the large batch sizes required mean development at this scale is time-consuming, expensive and not practical until the later stages of development.

In the development of a generic DPI treatment for asthma and COPD, a blend scale-up model was validated to demonstrate that it was possible to achieve comparable drug product performance from batches made at 500 g laboratory blend scale and batches made at 30 kg commercial blend scale. Figure 2 gives a comparison of the particle size distribution of the emitted dose for the two different scales and Figure 3 gives a comparison of the emitted dose at the two different scales.

Figure 2. Comparison of the particle size distribution of the emitted dose at two different scales measured by inertial impaction

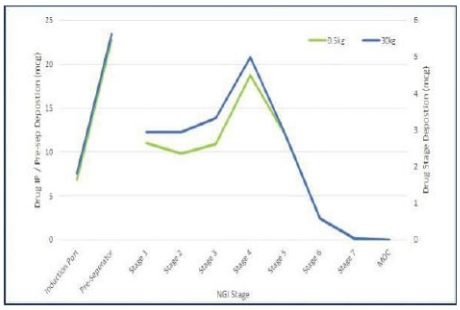
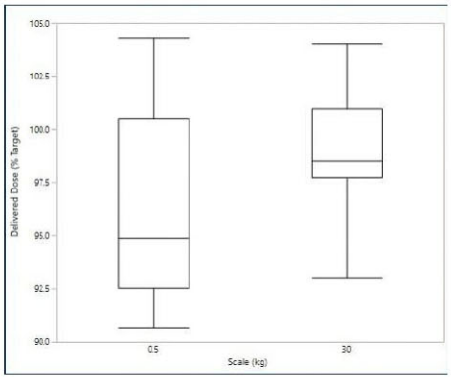


Figure 3. Comparison of the emitted dose at the two scales



This model enabled a significant amount of the development work to be conducted in the laboratory at development scale, minimizing material costs and enabling faster execution of experiments, and gave confidence in the ability to move up to the larger scale at a later date.

Minimizing the risks associated with the scale-up of manufacturing processes is key to developing successful products, and so the choice of equipment is important to be able to move seamlessly from laboratory scale to commercially-representative scale during the development and, ultimately, commercial-scale filling equipment.

Having the confidence in the ability to scale the process to commercial scale also meant that capital investment at the commercial supply manufacturing site could be made at a later development stage based on a risk-based approach for this project.

Case Study 3: Successfully Growing Volume and Continuous Improvement of a Commercial pMDI Product

Although in a perfect world, a development project would yield a well characterized commercially-ready device, process and formulation at the pivotal clinical stages of development, it is not until a commercial process has been bedded in, at the appropriate cycle times, and very many more batches manufactured with hundreds of thousands of devices being delivered to patients, that the product becomes more fully understood.

There are various elements that define success at the commercial stage. Clearly, being in a position to roll out a product in as many geographies in which it can be approved increases its access to patients and maximizes volume, and this volume may need to be responded to through scale-up. Maximizing volume usually provides opportunities to reduce costs and helps maintain a positive margin position even in adverse or competitive pricing environments. This accumulated know-how and experience of the commercial phase should be fed back to development teams to aid industrialization, minimize cost-of-goods, and build robustness into future products.

It is, therefore, vital for commercial success to maximize volumes and capacity, yields, process capability and efficiencies through synergies and economies of scale, and to maximize supply chain flexibility while minimizing risk, obsolescence, cycle times, downtime, costs and working capital. It is also essential to eliminate redundancy, waste and excess inventory over time.

Being active in the manufacturing and supply of a commercial product necessitates growing a global supply chain and procurement function within any development company. This function must manage the forecasting, logistics, cost management, contractual, and business continuity elements for the product with the company, ensuring that it effectively manages inventory including safety stock and distribution to its clients and ultimately to patients. This discipline and experience brings great value when managing situations that threaten to disrupt supply of critical medicines

In Conclusion

In conclusion, these case studies show how significant experience in all stages of the development life cycle, and applying the best technology solutions at each stage, can help organizations to successfully navigate an inhaled development program from feasibility through all stages of development and on to commercialization. The main considerations in picking the correct device or technology platform for a product are not only the needs of the patient and the disease treatment, but also looking at opportunities for accelerating the proof-of-concept or early clinical stages by using fast-to-clinic approaches. When these approaches are coupled with seamless scalability, through designing in manufacturability and choosing an appropriate manufacturing strategy, projects can be accelerated through later-stage development. In the commercial phase, the continued assessment and evaluation will enable the product to evolve, grow and maximize its potential through focused continuous improvement.

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Ms. Nikki Willis has worked in inhaled product development for over 30 years, and leads Vectura's pharmaceutical development department, responsible for dry powder inhaler (DPI) product development programs.