Using Phase-appropriate Delivery to Accelerate Inhaled Product Development

Different inhaled product development programmes can use different platform delivery technologies at various stages of development, and careful thought must be given as to what will work best at any given stage due to the broad choice of options.

To maximise the probability of success, delivery platform selection for each programme should be assessed individually so that the technical characteristics and the commercial drivers of each drug substance/ medicine are evaluated on their own merits. For a generic programme, there may be more constraints around the path to be followed, but outside of this area each new programme should be considered uniquely and it is important to bring as much experience as possible to selecting the appropriate delivery platform to progress the development, as well as to tackle the challenges that will inevitably arise along the way.

Device Choice

For inhaled products, the main platform delivery system approaches are dry powder inhaler (DPI), pressurised metered dose inhaler (pMDI), nebuliser devices and liquid spray inhalers. There are some other types of devices and/or formulation technologies that have niche applications, but are less commonly used.

For each main platform approach, there are further layers of choice sitting underneath and the pros and cons for each need to be understood in detail so that the final choice can be made. For example, under the general banner of DPI devices there is a choice to make between a unit dose device and multi-dose device, and then furthermore between a spray-dried dry powder formulation, or a traditional lactose blend. Even within the option of a unit dose device, there is the choice between a non-proprietary capsule-based inhaler, or a unit dose blister device and even if the developer has got to this point there are multiple device designs with different user interfaces, to further complicate the process of inhalation delivery technology platform selection.

Developers should try to adopt a device agnostic view, and then evaluate which platform (DPI, pMDI or nebuliser) is best for their particular candidate medicine, judging all the options impartially on their relative merits.

A basic commodity capsule-based inhaler can offer a flexible approach in the early stages of development, as different doses can be achieved via varying the formulation fill weight. This simple device type can deliver high doses of powder for a range of formulation types with good aerosolisation efficiency (formulation-dependant). On the down side, such devices typically offer no additional intellectual property (IP) protection to the product and have a more complex user interface than the multi-unit dose DPI devices.

Multi-unit dose DPI-based medicines have been shown to be hugely successful in the treatment of mild/moderate asthma and COPD and are quick and easy to use, highly portable and have the potential to offer additional proprietary protection to products.

pMDIs are also low-cost / high-volume devices with a generally universal user-friendly interface (simple "press and breathe"). Lung deposition is typically moderate, but the main limitation with this device type is the range of doses which can be delivered. With the increasing trend in the industry towards higher doses and high-cost biologic drugs, this is a delivery platform that can often rule itself out on both technical and commercial grounds.

Finally, nebuliser (especially smart nebuliser) devices are a higher-cost choice on account of their sophistication. It takes longer to deliver the medicine to the patient using these device types, but the range of doses able to be delivered can be much higher (up to tens of milligrams). Smart nebulisers are also capable of delivering high and deep lung deposition, and may be superior even to high-performing DPIs. Consistent, high and targeted delivery of a drug to the lung is obviously hugely advantageous and may increase probability of success in the early stages of development, and the process of formulation for nebulisation can be much simpler, especially if the molecule has good aqueous solubility.

Factors Affecting Device Development

As stated previously, starting from a "device agnostic" position really helps to facilitate the process of impartially evaluating the factors contributing towards the decision on the most appropriate platform for a given application.

Developers should start with the API-specific technical considerations, for example whether the drug is a small molecule or biologic; what the dose range is likely to be; and the physical properties of the drug, such as its solubility. All these aspects will have significant implications for device and formulation selection. Obviously, the user profile of patients who will take the medicine is also hugely influential, e.g., the age range of expected users; do they typically have dexterity issues; and can they follow complex user instructions. This can be a significant issue for both young and old patients. Additionally, the lifestyle of patients and their expectations around device use (e.g., portability) should also influence the choice. A device that is difficult to use, or is inconvenient for the target patient population, is much less likely to be used, with likely negative consequences on adherence, clinical trial outcomes and the ultimate success of any inhaled drug therapy.

Economics and commercial considerations also need to be looked at early on. The cost of goods for a device, and likely volumes, could rule out certain options, possibly not in the early stages of development, but certainly in terms of the final product to be commercialised. These factors need to be weighed up alongside the cost of the API, and whether the developer's ultimate strategy is self-commercialisation or to out-license to a larger partner post-proof of concept (PoC) and/or whether the intent is to manufacture in-house or outsource to a contract manufacturing

organisation (CMO). If the product candidate is a generic, the commercial considerations will also be significantly different than for an innovator (new chemical entity) product.

Finally, the disease and dosing regimen will impact the platform delivery technology selection decision: Is the medicine to be administered in a healthcare environment? (e.g., at hospital), or can it be taken by patients at home; how deep into the lungs must the drug reach for it to be efficacious?; and the number of doses the patient is required to take each day.

With all these factors to be taken into consideration, what may have worked for one product is unlikely to be transferrable directly to another. Often the drug molecule dictates what is possible, so some options can be excluded quickly based purely on technical considerations.

Very often, development programmes are purely focussed on the next milestone and value point inflection, so it is important to remember that the delivery platform does not necessarily have to be representative of the final commercial product – just "phase-appropriate", particularly in the early stages of development up to PoC.

Maximising the Probability of Success

The technology platform chosen must give the drug product the best possible chance of success. Although the factors previously discussed are numerous, in reality, a smaller number of considerations drive the majority of the decision-making.

The technical considerations are the most obvious: the drug molecule's properties are at the heart of any device and formulation selection and some preclude certain possibilities, for example, any need for a high dose (>1mg) would preclude the choice of a pMDI; or an antibody fragment would be very unlikely to be stable following jet nebulisation.

Minimising costs whilst working as quickly as possible is also likely to be hugely influential in any programme, so can impact development choices. If a molecule is freely soluble and stable in solution, complex formulation studies can be avoided and the drug can be delivered as a solution for nebulisation. If many different doses are required, varying volumes of a stock concentration can be nebulised, or a capsule DPI can be used and different formulation fill volumes of a standard dry powder formulation can be used to achieve the range of doses. The cost and availability of API material may also limit choices as wide development screening may not be feasible.

Finally, consideration must be given to maximising the probability of a successful clinical trial outcome. This may depend upon the efficiency of delivery to the correct area of the lungs, so more complex technologies such as smart nebulisation may be preferred over continuous nebulisation. Similarly, using a connected device that is able to gather information on patient usage will increase the confidence that patients have taken their medicine and have received the required dose effectively.

Making Informed Choices to Reduce Risk

Despite the large number of factors influencing the choice of delivery platform, being mindful of using phase-appropriate platforms can be crucial in reducing

risk, and saving time and money during development. There is the opportunity to change delivery platform between what has been used in the earlier stages of development in Phase I, or even up to proof of concept, and what ultimately might be commercialised.

This is a strategy increasingly being adopted by all organisations (not just small biotechs), focussed on getting into the clinic quickly to demonstrate the value of a candidate medicine. The ultimate commercial platform is of less concern at this stage, where the emphasis is towards ensuring that the platform can maximise deposition, offer dosing flexibility and minimise drug usage – thereby ultimately saving costs.

Either smart nebulisation, or the use of a simple commodity capsule DPI, lend themselves very well to this approach. These choices offer swift results and can demonstrate success so that milestones can be met in terms of funding or licensing. Depending on the strategy, projects developed in this method may then be transitioned to a multi-unit dose DPI for commercialisation, or progress all the way through to commercialisation with a capsule DPI or smart nebuliser.

Case Study: Accelerating a Small Molecule Developxment Programme to the Clinic

In a small molecule development programme for a niche disease, key influencing factors for the choice of delivery platform led developers towards selecting a hand-held mesh nebuliser. The drug molecule was very water-soluble and a broad dose range was required, making it potentially somewhat less amenable to being formulated as a DPI (although a capsule format might also have been suitable). For the disease indication, very high and deep lung deposition was needed to maximise the probability of success and minimise material consumption.

Despite being high dose (10mg), only approximately 100g of API material was required to undertake all the pre-clinical pharmaceutical development: including formulation development work, analytical method development and phase-appropriate validation, stability testing and product performance characterisation studies. Using the smart nebuliser, six different clinical doses (1–80mg) were able to be delivered via only two solution strengths. The programme was ready for the clinic in just 18 months.

Using smart nebulisation also offered the greatest potential to achieve high and deep lung deposition, and the mesh nebuliser in this case study also allowed consistent delivery, because the patient is guided by the device to take each inhalation the same. Additionally, the device has a very low drug retention rate (less than 10%), meaning drug substance usage is very efficient and wastage is minimised.

Conclusion

There is a large choice of platform delivery device and formulation technologies that can be used in the development of an inhaled medicine, and there are a number of factors that may need to be considered in order to decide which technology to exploit and advance. By taking a rational and methodical approach to each programme, the options can be narrowed down based on the molecule's properties to a smaller sub-set of factors in terms of technical needs, cost and time considerations, and maximising probability of success. It is important to remember that the platform decisions made to accelerate a programme to the clinic do not necessarily mean that the product is then defined throughout its lifetime. As shown in the case study, using a smart nebuliser or simple capsule device can allow for quick progression to clinical studies, but there are opportunities later on in development to change platform once milestones have been reached, as is appropriate for each particular product.

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