

RESPIRATORY MUCOSAL VACCINATION: HOW COULD WE DELIVER ANOTHER GLOBAL VACCINATION RESPONSE WITH CURRENT DEVICE TECHNOLOGIES?

Mark Parry of Intertek discusses the potential needs and opportunities for respiratory drug delivery devices in the context of a hypothetical global vaccination strategy, considering a variety of factors and how different respiratory device approaches could perform.

"THE CONTEXT OF DEVELOPING A GLOBAL VACCINATION STRATEGY PRESENTS CONSIDERATIONS WITH DIFFERENT PRIORITIES TO THOSE THAT HAVE DRIVEN DEVICE DEVELOPMENT TO DATE."

Devices for delivering small-molecule therapeutics via the nasal and inhalation routes represent a well-established pillar of the drug delivery sector. These technologies represent a range of solid- and liquid-based delivery systems that can be employed for effective delivery of therapeutics.

However, the increasing importance of large-molecule and biological drug products within the respiratory space over the past several years has spurred innovation and the development of new technologies to address key challenges. This progress is closely aligned with advancements in formulation science and delivery methods.

Looking towards the future, the context of developing a global vaccination strategy presents considerations with different priorities to those that have driven device development to date.

CONSIDERATIONS FOR A GLOBAL VACCINATION EFFORT

Target Population Size and Context

For context, let us examine one of the major respiratory targets: chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death worldwide, causing 3.5 million deaths in 2021 – approximately 5% of all deaths globally.¹ Estimates of COPD's prevalence in the population are around 10.4%,² although less than 6% of the population have been specifically diagnosed with COPD. The availability of COPD therapeutics is inconsistent across different regions, with the World Health Organization and other

researchers noting that inhaled medicines for COPD are poorly available and largely unaffordable in low- and middle-income countries (LMICs).

A new gold-standard COPD therapeutic would represent a massive new blockbuster product for the industry, which would create a need for investment in dedicated manufacturing capabilities and distribution. However, even that level of demand would be modest compared with the scale required for a global respiratory vaccination programme. Such a strategy could potentially represent a 20-fold or greater increase in target population compared with a hypothetical blockbuster COPD therapy.

Cost To Manufacture

Costs for covid-19 vaccines are somewhat difficult to define and, commercially, costs range widely across different markets; however, the cost of manufacture based on 100 million doses has been estimated to be between US\$0.54 and \$0.98 per dose (£0.40–£0.73).³

FluMist® (AstraZeneca) is one of the few respiratory vaccination products on the market and represents what is likely to be the simplest possible device option. The Centers for Disease Control and Prevention's (CDC's) wholesale costs are around \$18 per dose,⁴ compared with \$50–80 for current covid-19 vaccines, but retail costs are not a reliable guide to the exact cost of manufacture.

For a respiratory vaccine to be a competitive option versus traditional needle-based solutions, the cost of goods

"DRY POWDER-BASED DEVICES PRESENT A SIGNIFICANT OPPORTUNITY TO SIMPLIFY LOGISTICS AND REDUCE COSTS FOR THE DISTRIBUTION OF VACCINES GLOBALLY."

needs to adapt to the demands of the required scale. Every \$0.10 increase in the cost per unit means an increase in manufacturing costs of over \$8 million per 1% of the population treated.

Manufacturing Capacity

Manufacturing capacity for vials and prefilled syringes is well established, but the manufacture of covid-19 vaccines at a global scale still required a significant investment in increasing manufacturing capability.

Identifying a suitable device strategy requires consideration of what capabilities can be accessed both in-house and through contract services; realistically, however, most respiratory device forms would need investment in additional facilities to meet the demands of a global pandemic response. Identifying the best solution will require consideration of factors such as the scalability and the novelty of the technology used to understand its suitability for global scale-up.

Distribution and Cold Chain

Considering device technologies for respiratory vaccines based on the above points naturally leads to a consideration of solution-based formulations. A FluMist-style presentation allows for the use of existing prefilled syringe technologies and device parts that are relatively inexpensive. However, this approach will also have the same cold chain distribution needs as needle-based products.

Cold chain distribution costs are estimated to be 22 times higher than at ambient temperature, with cold chain distribution estimated to be a \$25 billion industry in 2025.⁵ In addition to this, covid-19 vaccine wastage in LMICs, where distribution is complicated by remote areas and varying cold chain equipment availability, was estimated to be as high as 30% in 2022.⁶

Dry powder-based devices present a significant opportunity to simplify logistics and reduce costs for the distribution of vaccines globally. This advantage could

potentially offset the likely higher manufacturing costs for these dosage forms, making them more competitive compared with traditional needle-based presentations – even given equal efficacy of the dose.

Self-Administration

One of the many challenges of a global vaccination programme using current delivery methods is the practicality of dose administration. Trained healthcare staff are required to deliver the vaccine, which necessitates the establishment of vaccination centres to meet the demands of vaccinating most of the population.

On the other hand, while support from healthcare personnel may still be the best approach for some patient groups, healthy adults would be capable of administering a respiratory vaccine to themselves, their children and any other people that they care for, such as elderly relatives. This would also be an advantage for remote distribution, where the demands on limited trained healthcare staff can be reduced.

FluMist has seen recent growth as a self- or caregiver-administered vaccine in the US, following its approval for this use

"ENGINEERING DRY POWDER FORMULATIONS PRESENTS AN ADVANTAGE IN DELIVERING INCREASED PRODUCT STABILITY, AS WELL AS OPPORTUNITIES TO SHAPE PARTICLE SIZES AND OPTIMISE DEVICE OPERATION TO TARGET DIFFERENT AREAS OF THE NOSE."

case in 2024.⁷ Monitoring the feedback and success of this first self-administered flu vaccine should provide a useful source for patient feedback in due course.

REVIEWING CURRENT DEVICE TECHNOLOGIES

Nasal Liquids

Liquid-based formulations are well served by existing nasal delivery device technologies, with uni-dose devices being an increasingly important class of nasal devices. Simple syringe-type options, such as those used for FluMist, are most likely to represent the lowest cost, while other options are available that use glass vials as the primary container/closure system, which may present stability and compatibility advantages and allow more sophistication in tuning of the aerosol plume. For example, the Narcan® nasal spray (naloxone hydrochloride – Emergent BioSolutions, Gaithersburg, MD, US).

Liquid-based nasal sprays can be considered active devices, where the patient does not need to co-ordinate activation and breathing, and are likely to be accessible to most age groups, as inspiratory effort is not a limiting factor.

Nasal Powders

Nasal powder devices are a growing space, with biologics fuelling part of this growth. Engineered dry powder formulations present an advantage in terms of increased product stability, as well as the potential to optimise particle sizes and device operation to target different areas of the nose.

Active devices that blow out the powder will have the advantage of not requiring patient co-ordination, making them easier for wide populations to use. This category of nasal powder devices, such as Baqsimi® (glucagon – Amphastar Pharmaceuticals, Rancho Cucamonga, CA, US), offers important delivery capabilities, though design complexity and cost considerations may limit their practicality for large-scale vaccination programmes.

Passive devices, such as the ICOone® nasal device (Iconovo, Lund, Sweden), have the potential to be lower cost products. However, these devices often require user effort and co-ordination to deliver a dose successfully and therefore may be less suitable for some population groups.

Inhaled Liquids – Nebulisers

Nebulisers are a common starting point for inhaled biologics as they are effective as a bridge between injectable and respiratory formulations, often providing the quickest route to clinical trials if a suitably stable formulation – or a reconstituted formulation – can be identified.

Convidecia Air™ from CanSino Biologics (Tianjin, China)* is a nebulised covid-19 vaccine using a similar formulation design to their needle-based vaccine, which may represent a more viable use case where a nebulised form is available for special population groups. However, nebulisers are not well-suited for mass vaccination, as the devices are expensive to distribute widely and not easily shared between users.

One potential model could be the use of nebulisers with disposable elements for each patient and dosing performed at vaccination centres or other healthcare settings. However, this would require similar logistical co-ordination to needle-based delivery with higher costs for the device aspects.

While nebulised delivery is not likely to be the most cost-effective route for large-scale vaccination, if advantages in efficacy are demonstrated and device designs are developed to support this usage model better, it is certainly achievable. However, it may be better suited as a complimentary formulation for specific patient groups.

Inhaled Liquids – Soft Mist Inhalers

Soft mist inhalers (SMIs) are a relatively new class of device are proving effective for delivering biologics in aqueous formulations with greater efficiency than nebulisers. These are similar to pressurised metered dose inhalers (pMDIs) in terms of needing user co-ordination but, with a softer and longer plume duration, it is easier for users to co-ordinate their inspiratory effort.

Unlike nebulisers, SMIs are not based on tidal breathing, which may present a greater opportunity to develop disposable parts, enabling multiple patients to use the same device. Again, individual disposable devices are unlikely to be cost effective with current technologies.

Inhaled Powders

Inhaled powders offer a broad range of device options, with devices available for both multiple- and single-use dosing. These are likely to present the most cost-effective option for individually disposable inhalers, but they do present their own challenges.

Dry powder inhalers (DPIs) are almost always passive and require inspiratory effort to administer the dose effectively, meaning that the use of DPIs is less common for children and some elderly populations. However, dose flexibility in vaccination may compensate for lower device performance in these more challenging populations.

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Pressurised Metered Dose Inhalers

Propellant-based pMDIs are commonplace in respiratory medicine; however, they have not been a focus for inhaled biologics due to challenges in finding formulation designs that ensure compatibility between the API, the propellant and the device.

pMDIs are unlikely to suit individual disposable device strategies, but they may be suitable for dosing multiple patients in a controlled setting with appropriate disposable parts.

One significant challenge with pMDIs is user co-ordination of breathing and dosing, as the dose is emitted within a second – user error in pMDI dosing is a significant obstacle for managing respiratory conditions. One solution to this is the use of a spacer that allows the patient more flexibility in breath co-ordination, making device co-ordination less critical.

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Disposable pMDI spacers already exist,⁹ such as the DispoZABLE® Spacer (Clement Clarke International, Mountain Ash, UK). These could provide a model for multi-patient dosing, but will add some costs and, again, would rely on dedicated vaccination centres rather than self-administration.

Manufacturing capacity for pMDIs is well established and could potentially respond to global demand if a suitable formulation strategy can be identified. For reference, in 2020, over 16 billion doses of salbutamol were sold in pMDIs in the EU, which accounts for more than half of the EU's total pMDI sales.¹⁰

CONCLUSION

Any global vaccination response will need to consider the science and efficacy, as well as the logistical practicalities, of any approach. The role of respiratory vaccination is still developing and, if it were the selected approach, would present challenges that the chosen device/delivery strategy would need to address.

Beyond this hypothetical discussion, respiratory vaccination is a developing area. Its potential advantages in efficacy and self-administration are likely to see significant development in formulation and device programmes in the coming years. Respiratory vaccines have the potential to become a critical component of global vaccination efforts, working alongside needle-based vaccines to strengthen pandemic preparedness and routine vaccination programmes.

ABOUT THE COMPANY

Intertek is a specialist contract orally inhaled and nasal drug product services provider, with GMP labs in Melbourn (UK), Manchester (UK) and Basel (Switzerland). The company's respiratory Centre of Excellence provides formulation development, performance testing, clinical manufacturing, impurities testing and extractables and leachables services. Intertek works with all the main inhaled and nasal delivery systems and has experience in both small- and large-molecule modalities. The Intertek team has over 35 years' experience working in the respiratory

space and has served companies all over the world. As an independent product developer, holding no intellectual property, Intertek helps its clients design products using optimal device and formulation technology from across the industry.

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Mark Parry has worked with Intertek for over 20 years since graduating from Cambridge University (UK) and currently works as the Senior Scientific Director, supporting the wide range of analytical, formulation, product development and research activities across the company. Mr Parry has worked in a range of pharmaceutical analysis and formulation development areas, with a particular focus on inhaled and nasal drug products. Mostly working in the pre-approval stages, Mr Parry's background includes extensive experience with product and formulation development, as well as method development and validation, IVBE studies, and pharmaceutical development activities for a wide range of clients across the pharmaceutical industry. Mr Parry is one of DDL's scientific advisers, a member or chair of several EPAG and IPAC-RS working groups, and an elected member of the RSC Inclusion and Diversity Committee. He routinely presents at conferences, as well as contributing to articles, research papers and posters on a range of respiratory topics.

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