NEW DRUG-NEBULISER COMBINATION PRODUCTS: CONSIDERATIONS BEYOND PERFORMANCE

In this article, `Nicolas Schwenck, Portfolio Manager eFlow Partnering, and Michael Hahn, Director eFlow Partnering & Strategy, both of PARI Pharma, summarise the critical success factors for bringing a new vibrating membrane nebuliser for a drug-device combination product to the market. They highlight opportunities and pitfalls – starting from the evaluation phase, through the development phase and finally during commercialisation.

In the business of developing new drug products for inhalation, one obvious fact is the necessity of a device which aerosolises the drug formulation such that it can be transported and deposited into the lung. This implies a decision on the device type and technology.

Nebulisers are currently the preferred device type for aerosol generation and delivery when it comes to new liquid drug introductions,[1,2,3] and vibrating membrane nebulisers (examples shown in Figures 1 & 2) seem to have recently taken a lead over jet and ultrasonic nebulisers.[4]

With the idea for a new treatment and drug formulation in mind, the pharma company starts looking for a suitable device capable of supporting early first-in-human studies (safety), followed by efficacy studies through to commercialisation and capable of fulfilling all the requirements arising from the different development stages. During a first screening phase, off-the-shelf available devices are tested *in vitro* and, preferably, a device manufacturer is contacted to prepare first steps for the development of an optimised drug-specific device configuration.

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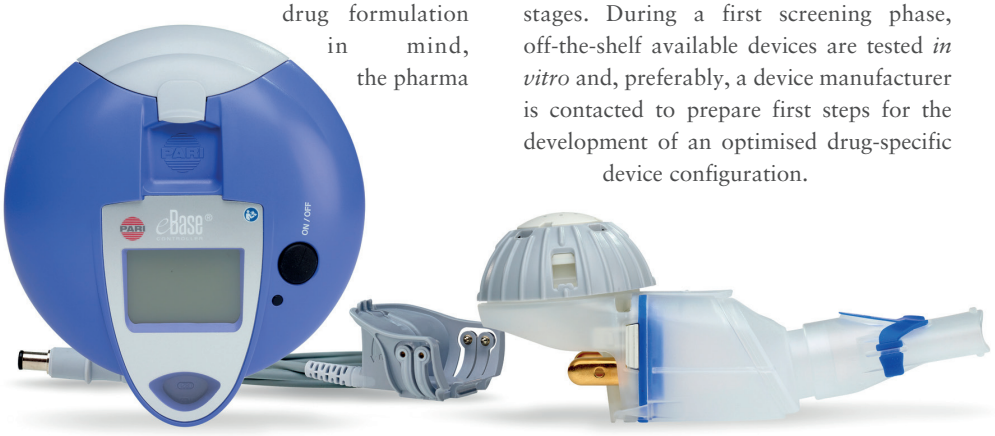

Figure 1: The eFlow Technology nebuliser – a vibrating membrane nebuliser.

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Figure 2: An eFlow aerosol head with the piezo-actuated membrane.

In the past, five established manufacturing companies provided high-quality membrane nebulisers to the market. Recently, the number of available membrane nebulisers for drug aerosolisation – i.e. with a relevant product and aerosol quality – has grown and more manufacturers have started entering the market.[3]

Their products differ in price, quality and technical features. Device concepts vary widely, even when leaving aside digital support features such as apps or smartphone-enabled expanded software capabilities or the potential to improve adherence with digital solutions,[5] which will inevitably become an integral part of future devices.

All membrane or mesh nebulisers are portable devices suitable for today's mobile lifestyle. Some devices have minimised size and weight, others use aerosol chambers with a valve system or breath-trigger modes to increase delivery efficiency. While all of these aspects are important for the device selection stage, long-term success of the newly developed drug product strongly depends on device reliability, ease of use and short treatment time.

That means, starting from a technical and performance aspect, there are several devices available and selection is complex. Not only do the available nebuliser products differ from a conceptual and technical point of view but also the business concepts of the manufacturing companies. Some offer general purpose systems, others drug-specific nebulisers with optimised performance and design, and a unique brand available for exclusive use with only one drug product.

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In the end, the clinical and commercial success of a new inhalation product does, of course, rely on the efficacy and safety of the drug – but it also depends considerably on the device adding the aspect of usability and, thus, on the combination of drug and device. This requires a strong collaboration between the pharma company and the device company.

EVALUATION AND SELECTION OF THE NEBULISER

The decisive factors for aerosol performance parameters are how much drug deposits in the targeted regions of the lungs and how much time is required to administer an efficacious dose. Another important aspect is the amount of drug which deposits in other regions – e.g. the upper airways or the environment – since this can have potential side effects. Special attention is required in the case of complex or fragile active pharma ingredients such as proteins, peptides or phages which may be negatively affected by the nebulisation process. Those target characteristics which are specified for the target patient population are tested during the various clinical phases.

As a first step, the pharma company chooses a device which is able to nebulise the new drug formulation properly with respect to nebulisation time, particle size distribution and a stable nebulisation process. This phase is often called the feasibility phase. During this phase, the drug formulation is nebulised for the first time. Standardised *in vitro* performance tests are conducted to determine the aerosol characteristics, and possible challenges with the nebulisation of the drug formulation can be identified early on.

The aerosol characteristics strongly depend on the formulation's physicochemical properties in combination with the nebuliser. There can be huge variations in the aerosol characteristics between various combinations of formulations and nebulisers. Every individual combination should therefore be characterised.[6] In order to optimise the aerosol characteristics, it may be useful, even at this stage, to adapt the nebuliser and/or the formulation.

Ideally, the drug formulation and the nebuliser are optimised together. However, in many cases the formulation is already developed and lengthy stability assessments and testing for potential toxicology, for example, are already underway. In such cases it is advantageous if the nebuliser technology is flexible and allows for multiple optimisation options solely on the device side – e.g. the aerosol droplet size distribution can be tailored by adjusting the pore size of the membrane rather than changing the formulation.[7] Three important steps during feasibility testing are shown in Figure 3.

It is thus recommended that the combination of drug and device be tested using the experience of a specialist laboratory. Some device manufacturers offer this testing as a service. The laboratory conducting the tests should have specific experience in testing drug-device combinations for inhalation products because, even during this early feasibility phase, relevant results for later Phase II and Phase III (take home) trials can be obtained to mitigate risks for those phases.

Furthermore, input from engineers as part of the feasibility team, with deep understanding of the device characteristics, can prove valuable in terms of device optimisation. Additionally, the combined expertise in testing methodology and execution, device development, and mechanical and electrical engineering can be complemented with knowledge of regulatory requirements and local registration procedures in major markets to make all the difference for a focused and accelerated start into a successful joint development project. In the end, all of this directly helps to minimise the development costs and timeline as well as raising the overall likelihood of success for the combination product.

Once the feasibility phase is concluded and an appropriate nebuliser meeting the technical requirements has been selected, the first preclinical testing – e.g. in disease animal models or toxicology studies –

Figure 3: During the feasibility phase – (top to bottom) NGI, breath simulator, and laser diffraction measurements.

is conducted. At this stage, the selected nebuliser design needs to be adapted to the study set-up and to the small tidal volumes of the animals for reproducible aerosol delivery. To overcome this challenge, some vibrating membrane nebulisers allow for the entrainment of the aerosol from the nebuliser to the animal in a controlled manner by means of a transportation gas flow – e.g. the Aeroneb Lab (Aerogen) or a special eFlow Technology (PARI Pharma) nebuliser.[8, 9]

Based on the toxicity results from animal studies, a Phase I clinical trial can be set up and first data in humans can be obtained to confirm safety including upper dose limits which, once again, demands flexibility in the design of the device to cover a broad dose range – e.g. by adjusting the fill volume or delivering acceptable aerosol for varying concentrations.

The evaluation phase concludes when the pharma company has selected a device company and the respective nebuliser. At this stage, it has been confirmed that the nebuliser meets those aerosol characteristics which are predicted to result in the optimal deposition of the aerosol in the target region of the respiratory tract. Such characteristics are identified based on pathological considerations as well as current expert know-how in aerosol science, based on or described in the literature.[10-13]

The actual proof is obtained later when the drug-device combination enters Phase II clinical trials where appropriate primary end points must be met to demonstrate efficacy. Following the evaluation phase, the actual development of the specific drug-device combination product is conducted.

In the remainder of this article, we highlight and discuss some important aspects of device development as shown, for example, for the investigational drug-device combination products described in the literature[14,15] and the subsequent commercialisation after approval. These aspects go well beyond technical considerations but are similarly critical for the success of an inhaled product.

DESIGN CONTROL

Both the US 21 CFR part 820 and ISO 13485 require medical device developers and manufacturers to implement a comprehensive quality management system (QMS) as a basis for later approval documentation of the device (e.g. the NDA of the combination product or the technical

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documentation according to the European Regulation (EU) 2017/745 commonly known as the Medical Device Regulation). Part of this QMS is a proper design control and the creation of a design history file to document the development process of the device as part of the combination product.

The starting point for design control is the set of user requirements which is translated into technical means in the design input requirements. The design's validation and verification experiments, respectively, provide evidence that the nebuliser meets both user and design input requirements. Additionally, a clinical evaluation and risk management plan needs to be designed and implemented.

All these steps require close collaboration between the pharma company and the device company. In particular, human factors evaluation as part of risk management plays a special role in the development process emphasised by the US FDA guideline Applying Human Factors and Usability Engineering to Medical Devices issued in 2016 as well as the IEC62366.[16]

The consideration of usability is important early on in the development process in order to implement the respective studies into the overall development plan of the drug-device combination product. If human factors engineering is not carried out properly at the right time, it may result in significant delays.[17] As the human factors evaluation has to be carried out with an appropriate sample of patients from the intended target patient population, this step can only be carried out with the final device for the specifically designated patients.

Human factors is another area for a joint effort by the pharma and device companies. Human factors specialists on the device developer side can provide their experience in designing and conducting efficient human factors studies in compliance with guidelines as well as with current thinking of regulatory bodies. An exemplary human factors evaluation process was the use and optimisation of the eFlow Closed System specifically for elderly COPD patients.[18]

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DEEP REGULATORY KNOWLEDGE AND TRACK RECORD

In addition to technical and design control challenges, a deep understanding of the regulatory requirements for both drug products and medical devices is crucial. In many cases, pharma developers have such regulatory understanding for drug products but are less knowledgeable with respect to medical device regulations in different territories. Experienced device manufacturers can complement the pharma developers with their regulatory know-how.

Since these device companies are typically active in several projects simultaneously, they frequently interact with regulatory authorities over many years and understand both the guidelines and the interpretation by the relevant authorities. Furthermore, the device manufacturers have a great interest in providing coherent and appropriate information to regulators on the device technology across different projects. If a selected nebuliser manufacturer has such extensive experience with regulatory authorities, pharma companies substantially mitigate the regulatory risk coming from the device.

RELIABLE DEVICE MANUFACTURING CAPABILITIES AND SUPPLY

By far the most expensive part of the development of a drug-device combination product is the clinical trials. Nowadays, during development of an inhaled

Figure 4: Reliable device manufacturing capabilities are crucial for commercial success.

combination product, companies use just one rather than several nebulisers to minimise both costs and the risk inherent in clinical trials. Thus, safety and efficacy are established for a product only with one specific delivery device which becomes part of the label of the combination product. The pharma company therefore depends, for both clinical development and after approval, on the availability of the respective nebuliser in the required quality and quantity.

Figure 4 shows strongly quality controlled and highly automated production facilities. Poor or variable device performance due to quality issues may impair results of clinical trials. In particular, when novel device technologies are used which are not yet produced at a relevant commercial scale, the manufacturer may have a limited knowledge of the production process variability and appropriate quality assurance tools which many pharma companies consider a severe risk for their development. Furthermore, timely availability of high-quality nebulisers is mandatory in order to stick to tight project timelines.

The number of nebulisers required to conduct preclinical and clinical development is quite small. This quickly changes as soon as launch preparations start. Well ahead of the anticipated approval date, pharma companies prepare for launch by ordering drug product and devices to de-risk the actual launch and create a considerable safety stock based on their forecasts. This significantly increases the demand for nebulisers before approval and may require scale-up efforts.

Once the launch is successfully mastered, a stable and reliable production, change control process and supply chain for the device must be in place to guarantee market supply and to recoup development and marketing investments into the drug-device combination. For pharma companies this means their commercial success relies on a single source for the critical device component of the product.

Thus, in a professional device selection process, pharma companies – in addition to technical and clinical requirements – add process variability, manufacturing and quality management capabilities to their checklist when they select a nebuliser partner for the development and commercialisation of the combination product in order to mitigate their risk. A relevant track record of the device manufacturer is a positive indicator for such important additional attributes.

ORGANISATIONAL STRUCTURE AND STRATEGIC ORIENTATION

All previously outlined capabilities come with high complexity involving many disciplines and organisational functions which increase with progressing clinical development and require a tight and open collaboration between the pharma partner and the device partner. A deep and trusting collaboration is crucial for the success of every project. Accordingly, proficient pharma companies evaluate the organisational structure and skill set of the device partner when they select a delivery device for their drug product. The high development risk of an inhaled drug-device combination product and the initial low quantities of nebulisers needed to conduct clinical trials presumes a mutual long-term strategic interest of the device manufacturer and the partnering pharma company.

INTELLECTUAL PROPERTY AND EXCLUSIVE COLLABORATION

The development of inhaled drug products is a process which is long, risky and resource intensive. Hence, once regulatory authorities approve a product, it is important for pharma companies to strengthen the competitive position of a product beyond superior safety and/or efficacy. The most common form of intellectual property protection in this industry are patents which usually expire 20 years after they are filed. However, as patents are filed relatively

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early during development, the development time needs to be subtracted from that 20-year period when it comes to economic considerations.

Effective patent protection of a combination product may be based on claims for the drug product, the device or the combination of both. Of course, in order to benefit from device-related patents, the pharma company must have exclusive rights to such patents (e.g. via a licence from the device developer) for use with their drug product. This includes proprietary technological and manufacturing know-how and expertise which are essential to ensure the drug-device combination is a success in the market.

In the US, the marketing authorisation holder of the drug product may choose to list patents which protect the approved product in the FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the Orange Book). Until the expiry of patents validly listed in the Orange Book, the agency will not approve a generic product under an ANDA.

In some circumstances, even patents on the device may be eligible for the Orange Book listing if the marketing authorisation holder has the (exclusive) right to reference such patents.[19] Additional market exclusivity mechanisms may apply, such as under an orphan drug designation or if a product is considered a "qualified infectious disease product" under the Generating Antibiotic Incentives Now Act.

If an optimised nebuliser with highly specific delivery characteristics is used in the pivotal clinical trials, it is also required that such a device be used after approval. The regulations for generic drug products – e.g. in Europe according to article 10.1 of the Directive 2001/83/EC or an abbreviated application according to article 10.3 of the same law – require the same delivery performance of the test and the reference product.[20] If the reference product uses a nebuliser with a unique delivery performance, it may be very difficult to copy such a reference product. This is also recognised by the FDA as the agency stated in relation to the approval of the first generic of Advair: "The FDA recognises challenges companies face when seeking to develop hard-to-copy complex generics, such as drug-device combination products, including when the drugs are incorporated into inhalation devices like this."[21]

Hence, the exclusive collaboration (including an exclusive licence to device patents, technological and manufacturing know-how and expertise, and an exclusive supply relationship) between the device manufacturer and the pharma company can be an important part in the protection strategy for an inhaled product.

CONCLUSION AND OUTLOOK

Compared with other dosage forms, the development of inhaled drug products is particularly risky and many products fail during development.[22] The reasons for the disproportionately high failure rates of respiratory drug development may be multifactorial and can be partly caused by complexity.[23] Not only the drug product needs to be developed but also a suitable device. Thus, in order to reduce the risk of inhaled drug development, experienced pharma companies conduct a proper due diligence not only on the device technology but also on the company which develops and produces the devices.

Risk mitigation for a nebulised drug development project involves close collaboration with a competent device partner offering a high-performing and reliable nebuliser technology which can be flexibly adapted to the formulation, a record of accomplishment. The device partner must demonstrate both the capability – e.g. staff with expert know-how, resources, manufacturing infrastructure and quality management systems – as well as the strategic commitment to partner with pharma companies to support and endure the long-lasting drug development process.

The device patent portfolio and an exclusive collaboration with the nebuliser manufacturer may be part of the protection strategy for an inhaled product and together help pharma companies to recoup the significant investments needed for its development and marketing.

ABOUT THE COMPANY

PARI Pharma develops and manufactures optimised eFlow Technology nebulisers in co-operation with, and for, partners from the pharma industry. Pharma companies developing innovative drugs for inhalation approach PARI because of its experience in drug and device development. The eFlow Technology platform is suitable for a wide range of patient populations and drug formulations. It enables short development times for nebulisers optimised for specific medications. PARI has a committed team with a considerable track record. As of today, five commercial drug-specific eFlow Technology nebulisers administer specific inhaled medications.

REFERENCES

1. *Elphick M et al, "Factors to consider when selecting a nebulizer for a new inhaled drug product development program". Expert Opin Drug Del, 2015, Vol 12(8), pp 1375–1387.*
2. *Martin A, Finlay W, "Nebulizers for drug delivery to the lungs". Expert Opin Drug Del, 2015, Vol 12(6), pp 889–900.*
3. *Pritchard J et al, "Mesh nebulizers have become the first choice for new nebulized pharmaceutical drug developments". Ther Deliv, 2018, Vol 9(2), pp 121–136.*
4. *Pritchard J, "Nebulisers: Time to Reinvent the Wheel". ONdrugDelivery Magazine, Issue 92 (Nov 2018), pp 10-15.*
5. *Koehler Y, Fuchs C, "Monitoring Nebuliser Usage & Lung Function in Clinical Trials". ONdrugDelivery Magazine, Issue 87 (Jun 2018), pp 66-70.*
6. *Denk O et al, "Meeting Formulation Challenges for Reproducible Delivery Using eFlow® Technology". Proc RDD Europe, 2013, Vol 1, pp 163–174.*
7. *Knoch M, Keller M, "The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems". Expert Opin Drug Del, 2005, Vol 2(2), pp 377–390.*
8. *Mitchell J, "Abstracts from The Aerosol Society Drug Delivery to the Lungs 20 Edinburgh International Conference Centre Scotland, UK December 9–11, 2009". J Aerosol Med Pulm D, 2010, Vol 23(6), pp 415–440.*

9. *Tservistas M et al, "A Novel Nebulizer Based on eFlow® Technology can Simultaneously and Efficiently Administer Aerosolized siRNA Formulations and Supplemental Oxygen for the Treatment of RSV in Infants". 20th Drug Delivery to the Lungs Conference, December 2009.*
10. *Lizal F et al, "Development of a realistic human airway model". Proc Inst Mech Eng, Part H: J Eng Med, 2012, Vol 226(3), pp 197–207.*
11. *Finlay W, "The mechanics of inhaled pharmaceutical aerosols: an introduction", 2nd Edition. Academic Press (Publ), June 1, 2001.*
12. *James A et al, "The respiratory tract deposition model proposed by the ICRP task group". Radiat Prot Dosim, Vol 38(1–3), 1991, pp 159–165.*
13. *Schwenck N, "Aerosol characterization for the development of novel inhalation devices: in vitro experiments". SimInhale COST Action: Int Conf on Current Challenges and Future Opportunities for Inhalation Therapies, 2019.*
14. *Gessler T et al, "The safety and pharmacokinetics of rapid iloprost aerosol delivery via the BREELIB nebulizer in pulmonary arterial hypertension". Pulm Circ, 2017, Vol 7(2), pp 505–513.*
15. *Li Z et al, "Development and inhalation properties of Amikacin Liposome Inhalation Suspension (ALIS) for treatment of Mycobacterium avium complex (MAC) lung infections". Drug Delivery to the Lungs Conference, Dec 2019.*
16. *"Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration Staff". US FDA, 2016.*
17. *"scPharmaceuticals Receives Complete Response Letter". Press Release, scPharmaceuticals, June 13, 2018.*
18. *Gallem T, "The eFlow 'Closed System' (CS) – A Novel Device Platform For Liquid Aerosol Drug-Device Combinations". ONdrugDelivery Magazine, Issue 50 (Jun 2014), pp 13-16.*
19. *"Approved Drug Products with Therapeutic Equivalence Evaluations". US FDA Orange Book, 2020.*
20. *"Guideline on the requirements for clinical documentation for orally inhaled products (oip) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents". Adopted Guideline, EU EMA, January 22, 2009.*
21. *"FDA approves first generic Advair Diskus". Press Release, US FDA, Jan 30, 2019*
22. *Mestre-Ferrandiz J, Sussex J, Towse A, "The R&D cost of a new medicine". Research Report, Office of Health Economics, Dec 2012.*
23. *Barnes P et al, "Barriers to new drug development in respiratory disease." Eur Respir J, 2015, Vol 45(5), pp 1197-1207.*

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Michael Hahn heads up a team of business development, contract and portfolio managers. It is key for these functions to build and maintain long-lasting relationships with PARI's pharma partners. Mr Hahn joined PARI in 2006 and held different positions in research and development, and business development, with increasing responsibility. He earned a master's degree in Electrical Engineering and an MBA, both from Technical University of Munich (Germany).