Overlooked opportunities for nebulizers in inhalation product development

Nebulized medication use is growing faster than that of inhalers, yet most companies focus on bringing new inhalers to market. What opportunities might they be missing?

John N. Pritchard, PhD
Respironics Respiratory Drug Delivery

An introduction to nebulized therapy

The popularity of the nebulizer as a means of delivering aerosolized medication has varied in the 150 years since its inception. Before the advent of the pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI), the nebulizer was the main method of administering aerosolized drug to the lungs. But the increased portability and convenience that pMDIs and DPIs provided has resulted in reduced popularity for nebulizers in recent decades. Nevertheless, the ability to deliver therapeutic doses of drug to patients utilizing their normal tidal breathing is a fundamental attribute that has given the nebulizer universal applicability in the delivery of aerosolized medication to all groups and types of respiratory patient. It avoids undesirable situations, such as that of very young children unable to understand instructions to inhale upon command, or that of older or physiologically impaired patients not able to perform the fast/slow/deep breathing maneuver required by inhaler devices such as DPIs and pMDIs. This may also explain the enduring popularity of nebulizers in emergency departments, where the treatment of asthma exacerbations has been shown to be equally achievable with a pMDI and an add-on valved holding chamber,[1] but where the use of nebulizers has remained widespread.[2,3] Use in a hospital setting may create a perception in the patient mind that nebulized treatment is the most effective since it helps them recover when they are feeling at their worst. This also may give them additional confidence to persist with this form of treatment when they return home.[4,5] Other advantages of treatment via nebulizer include the obvious indications that the device is generating aerosol and that drug administration is complete.

Nebulized therapies are typically prescribed for young children with asthma and for elderly and very sick patients with asthma and chronic obstructive pulmonary disease (COPD). Thus, the most commonly prescribed drugs are short-acting β-agonists or anti-muscarinics, alone or in combination, together with corticosteroids in pediatric asthma. Other nebulized drugs include antibiotics, saline and DNase for treatment of cystic fibrosis and prostacyclin for pulmonary arterial hypertension. Corticosteroids, particularly budesonide, are the largest-selling class of nebulized drug by value, comprising over 50% of the total nebulized drug market in the United States.[6] Indeed, nebulized budesonide generates the most revenue of any inhaled drug in China, including drugs administered via pMDI or DPI; however, this reflects the price per dose. By number of prescriptions, short-acting bronchodilators dominate, accounting for over 80% of prescriptions for nebulized medication in the US.

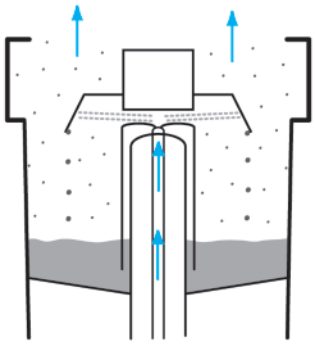
It has been estimated that, in 2015, approximately 7% of inhaled doses were taken by nebulizer, and that between 2011 and 2015, the number of nebulized doses used were growing faster than either that of pMDIs or DPIs.[7] This may not be surprising, considering the increases in global life expectancy (an increase of 5 years between 2000 and 2015) and the associated rise in prevalence of COPD.[8,9] That prevalence is particularly relevant to nebulizer use as, among the three principal types of aerosol delivery devices (nebulizers, DPIs and pMDIs), the nebulizer is the device most suited to delivery of aerosol to the more severe COPD patient. Such patients may be elderly and have degraded fine motor skills, dexterity and hand muscle strength, which can inhibit the correct use of inhalers.[10] Therefore, it is not unexpected that 50% of patients discharged from a hospital after an COPD acute exacerbation are prescribed nebulized drugs,[11] most commonly a combination of short-acting β-agonist and muscarinic drugs.

Despite this, the large majority of new treatments recently brought to market have been developed in portable inhalers.[12] Yet recent developments in nebulizer technology, along with the relative ease with which solu-

Figure 1

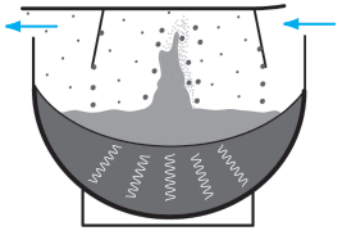
Schematic representations of nebulization via jet, ultrasonic and mesh nebulizers

Jet nebulization



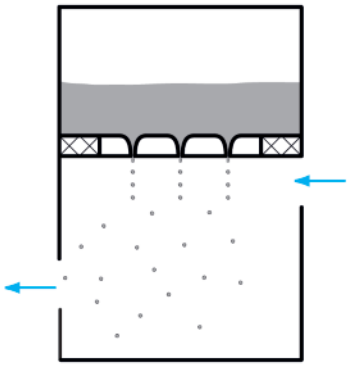
Aerosol generated by the breakup of a fast moving air/liquid mixture; larger droplets impact on baffles and are returned to the bulk fluid; smaller droplets exit the nebulizer for inhalation.

Ultrasonic nebulization



Aerosol generated at the peak of a fountain created by focused ultrasonic waves; larger droplets impact on baffles and are returned to the bulk fluid; smaller droplets exit the nebulizer for inhalation.

Mesh nebulization



Aerosol generated when columns of fluid are extruded from small mesh holes and break up to form aerosol droplets; droplet size is related to hole size; droplets exit the nebulizer for inhalation.

tion formulations of drugs can be developed for nebulization, have led to a number of largely overlooked opportunities for nebulization as a means of delivering drugs. This article will highlight some of these opportunities and the reasons they have come about.

Nebulizer technology

Nebulizer technology available to patients today consists of jet, mesh and, to a lesser extent, ultrasonic nebulizer devices (Figure 1). Of these, the most widespread is the jet nebulizer, which relies on a source of compressed air to create a respirable aerosol. Nonetheless, the conventional jet nebulizer also has disadvantages. Bulky size, the requirement for a grid-connected power supply and noisy operation lasting 6 to 15 minutes for a fill of 2 to 5 mL of liquid for each treatment are significant considerations for the patient, compared with one or two puffs taken from a DPI or pMDI. Treatments can add up to a significant burden upon a patient's free time and quality of life, and the requirement to carry a bulky compressor and associated leads and tubing may not fit well with the active lifestyles of many patients. Ultrasonic nebulizers that generate aerosol by means of focused ultrasonic waves within the nebulizer liquid (Figure 1) improved the size and noise issues inherent in jet nebulizers, but were associated with additional disadvantages, such as inefficient nebulization of suspensions and heating of medication during nebulization that could damage thermolabile drugs. Both jet and ultrasonic nebulizers are also inefficient, continuing to generate and thereby wasting aerosol while a patient is exhaling. The efficiency of jet nebulizers has been improved slightly with the introduction of breath-enhanced models that boost output during the inhalation phase of breathing. In addition, breath-activated jet nebulizers provide even higher efficiency, but with increases in nebulization time and reduced applicability. Their use should be confined to older children and adults to ensure sufficient inspiratory force to activate the mechanism.[13] Despite such improvements, these nebulizers still retain approximately 1 mL of the medication at the end of treatment, which will go to waste. All of these issues have led to the nebulizer becoming the least common of the three main delivery technologies (nebulizer, pMDI and DPI) used to deliver aerosol therapy.

However, the most significant of these disadvantages are now being addressed with the increasing adoption of mesh nebulizers, which offer battery-operated portability and rapid, quiet operation. In mesh nebulization, medication is aerosolized in a single pass through the mesh (Figure 1) without needing classification via the baffles used in jet and ultrasonic nebulizers, which return oversize aerosol droplets to the medication reservoir. This can result in greater efficiencies in time, energy expenditure and volume delivered. The latest generation of mesh nebulizer can be expected to operate with treatment times of around 4 minutes and residual volumes of about 0.3 mL.[14] Improvements in the manufacturing process include the optical assessment of meshes to ensure that particle sizes and treatment times the patient experiences are consistent, even after replacement of the mesh.[15] Treatment burden can be further reduced, as the new generation mesh of nebulizers can be expected to be easier to use and clean.[16] Ease of cleaning may be particularly relevant to mesh nebulizers, as treatment time may be prolonged due to blockage of some nozzles if the

mesh is not cleaned according to manufacturer instructions.[17] When developing suspension formulations for nebulization, it is important to consider the size of the drug particles that make up the suspension. Given most drug particles are asymmetric in shape, it is the size along the smallest axis that is most critical. Therefore, suspensions of budesonide are able to be used successfully with many mesh nebulizers despite having a volume equivalent diameter similar to that of the nozzle due to their asymmetric shape.

Continuity of care can be accomplished by using the same mesh aerosol generator to fit both the ventilator circuit and an add-on aerosol holding chamber, with mask or mouthpiece, for use in the emergency room and in a portable nebulizer at home.[18] Thus, within the market for nebulizers, market research reports show that sales of mesh nebulizers are expected to grow faster than jet and ultrasonic types of nebulizer.[19]

Nebulizers in the development process

From a pharmaceutical perspective, formulation of a new drug for nebulization is relatively straightforward, with addition of surfactants to stabilize a suspension if the drug is insufficiently soluble to form a stable solution. This can either be provided in bulk, as for hospital use, or as individual doses, usually in a blow-fill-seal container. However, it does require manufacture under aseptic conditions, which will add to the manufacturing complexity. Alternatively, the drug can be supplied as a unit dose dry powder for reconstitution with water before use. The relative simplicity with which a liquid formulation can be developed means it can be created rapidly and with minimal amount of drug substance, when the drug is at its most expensive to produce. This is in contrast to a pMDI or DPI inhaler, which will require formulation of inhalable particles with the propellant/carrier and demonstration of pharmaceutical performance of the drug delivered by the inhaler. Furthermore, inhalers need to be shown to maintain performance at end-of-shelf-life before going into a clinical trial, whereas nebulized formulations only require physical and chemical stability of the formulation to be demonstrated. Many nebulizers can be used with up to 8 mL of liquid, which makes them particularly suitable to administer high doses of drug during the early stages of clinical development, when the maximum tolerated dose needs to be established. This is because the devices are designed to operate with normal tidal breathing so patients tend not to tire if the size of the dose requires treatment times in excess of 10 minutes. At the other end of the scale, there are small volume (50-300 µL) mesh devices in development that, for drugs that can be formulated in concentrated form, can deliver a dose in one to six breaths, thereby simulating inhaler delivery, but with the advantages of a liquid formulation.[20]

Furthermore, mesh nebulizers/devices are particularly suited to the delivery of macromolecules, as they subject the formulation to relatively low shear, liquid passes through the orifice only once and there is no heating of the formulation. These factors combine to retain the three-dimensional structure and biological activity of the molecule. The ability to select meshes during the manufacturing process that produce specific mass median aerodynamic diameters (MMADs) for the aerosol distributions may also allow greater targeting of aerosols to specific regions of the airways and lungs from mesh nebulizers.[21] Along with delivery of aerosol boluses and controlled flow,[22] this may be useful in the development of drugs that have a narrow therapeutic window between efficacy and the onset of side effects.

As a result, nebulizers are often used in Phase I and IIa trials, where there is still high clinical risk associated with the investigational drug, so the expense of developing a more complicated and costly DPI or pMDI inhaler formulation can be avoided. Dosimetric, breath-activated, mesh nebulizers can be used to deliver reproducible doses with little waste and so are ideally suited for dose-ranging studies and instances when the quantity of drug manufactured for early studies is low. More recently, breath-actuated mesh nebulizers, including those incorporating data logging capability, have been used in clinical trials and have provided useful data to explain anomalous patient results, for example, a lack of exposure explainable by failure to adhere to the treatment regimen.[23] Furthermore, if remote monitoring is used while the trial is underway, adaptive trial designs can be used to exclude non-adherent patients.[24]

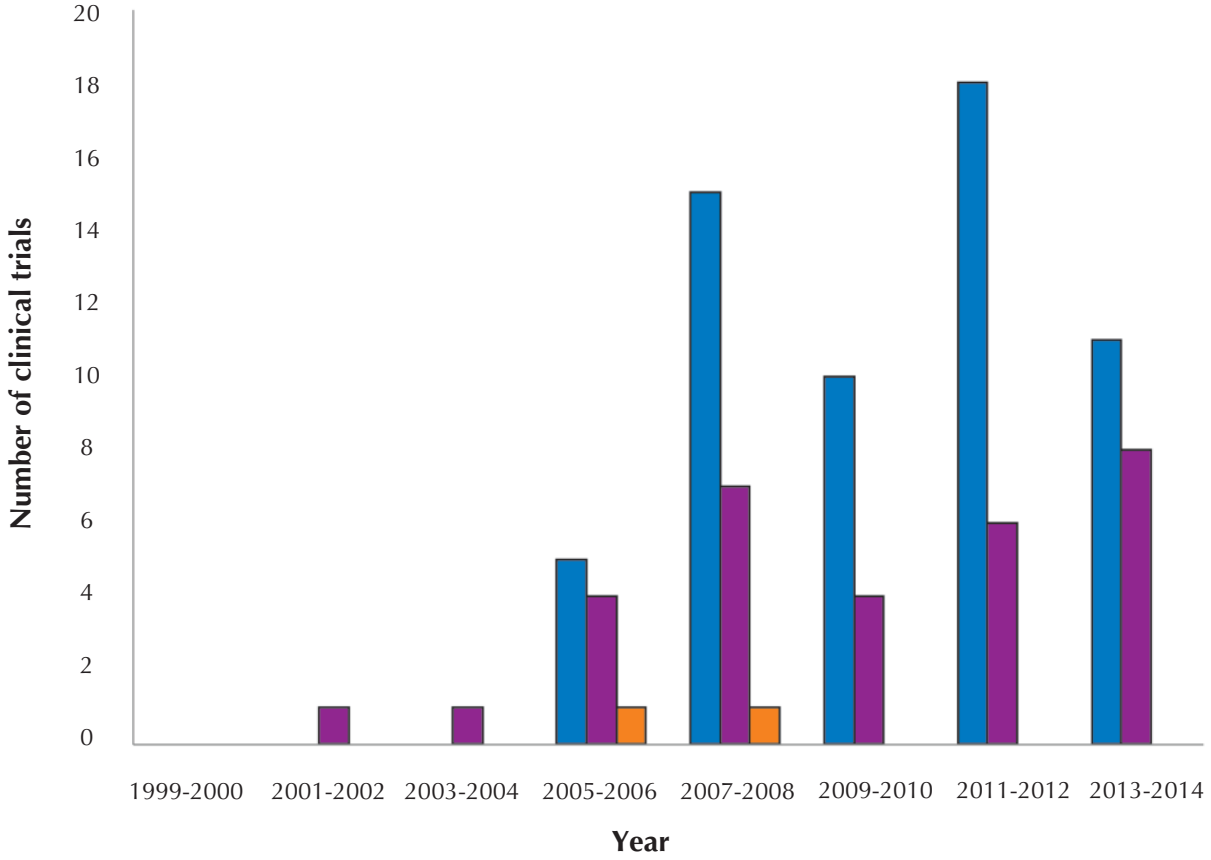
Evidence for the increasing adoption of mesh technology can be found in an examination of clinical trial registers,[25, 26] established in the US in 2000 and the EU in 2004. A search of US and EU clinical trial registers undertaken in January 2015, showed that between 2005 and 2012, mesh nebulizers were used in 53% of valid studies, while the use of jet (44%) and ultrasonic (3%) nebulizers was lower. (Studies were considered valid if they were clinical trials involving nebulizers with the following excluded from the analysis: nebulizer not specified, study withdrawn, study not a drug trial or for non-inhaled drugs, study investigated hypertonic saline or heliox, scintigraphy, provocation tests, used spinning-top aerosol generators or nasal delivery.) Examination of the clinical trials in terms of sponsorship showed that mesh nebulizers were favored over jet nebulizers in clinical trials sponsored by pharmaceutical companies as opposed to clinician-sponsored studies (Figure 2). The three most popular models of mesh nebulizer were the I-neb AAD System (Respironics Respiratory Drug Delivery [UK] Ltd, Chichester, UK), Aeroneb Go (Respironics Respiratory Drug Delivery [UK] Ltd, Chichester, UK), and eFlow (Pari GmBH, Starnberg, Germany), and all were available on the market by 2004.[27-29]

Demonstrating nebulizer performance

Historically, there has been a substantial difference in performance between some of the best and worst nebu-

Figure 2

Clinical trials sponsored by pharmaceutical companies registered by year between 1999 and 2014 that used mesh (blue), jet (purple) or ultrasonic (orange) nebulizers



lizer systems on the market.[30,31] However, as drug discovery and development becomes more targeted and new pharmaceutically active drugs are developed, dose control will become more important. This is already being seen in increased restrictions by regulators, such that modern drug approval is related to the specific nebulizer used in the later phases of a clinical trial program, with an advisory in the instructions for use of the launched product stating that the performance of other devices has not been evaluated.

For general-purpose nebulizers intended for use with existing drug formulations, a manufacturer must document the performance of the new nebulizer device according to the results of tests defined in test standards.[32-34] The tests and parameters defined in the standards offer simplified test model approximations of the fate of aerosol droplets/particles, to balance practicality of the tests with relevance to the clinical situation. Recent work has shown an area of improvement that seems practical and may be of increasing importance in the delivery of modern pharmaceuticals for which dose is likely to be more of a factor. Hatley et al. showed the impact of varying the inhalation:exhalation (I:E) ratio of the simple model of the breathing cycle used in the test standards upon the delivered dose and respirable delivered dose from nine different brands of nebulizer with five different modes of operation (conventional jet; venturi jet; breath-enhanced jet; mesh; and breath-activated jet/mesh).[34] The results showed the usual wide variation (up to 2.5 times difference) in delivered dose and an even greater, four-fold difference in respirable delivered dose between the different nebulizers, when using the test breathing pattern mandated in the standards. But there was also a reduction of up to 60% in respirable delivered dose from non-breath-activated nebulizers when tested with breathing patterns defined in the standards, compared to a breathing pattern typical of a patient with severe airflow obstruction/restriction. In contrast, the breath-activated jet nebulizer demonstrated only a 10% change in the respirable delivered dose over the same range, while the respirable delivered dose from the breath-activated mesh nebulizer was independent of I:E ratio, although the treatment time from both breath-activated nebulizers was significantly increased, providing further evidence why mesh nebulizers, particularly breath-activated models, are more suited to drug development.

Neglected opportunities for nebulized therapies

For the 50% of COPD patients who are discharged from the hospital with a nebulized drug, they may find themselves switched from a once-daily, anti-muscarinic inhaler to a four-times-per-day nebulized combination of short-acting β-agonist and anti-muscarinic, with a consequent significant increase in treatment time. It is well documented that burden of disease can adversely affect adherence[35] and it has been estimated that a reduction in adherence of 20% leads to an increase in

adverse events of more than 10% in COPD patients.[36] It is therefore not surprising that patients are less likely to be readmitted when prescribed a long-acting, nebu-lized β-agonist, compared to a short-acting product.[37] Consequently, development of long-acting, nebulized β-agonists and anti-muscarinics represent a significant unmet therapeutic need,[38] a gap one author described as a "compelling opportunity."[11]

Nevertheless, this opportunity has been largely overlooked to date. It has been suggested that this is due to unfavorable commercial considerations.[38] Once proof-of-principle is achieved, the nebulized formulation is normally dropped in favor of continued development of the drug in a pMDI or DPI form to serve the majority of patients. After the pMDI or DPI product is marketed, a nebulized product may be considered as a lifecycle opportunity, but since this is a completely different delivery system and formulation requiring its own dose-ranging and pivotal Phase III studies, introduction to the market can take five years or more. By that time, little of the original drug patent life may remain, so unless for-mulation patents can be obtained, there is insufficient time to recover the investment before generic copies enter the market. One potential way around this would be to develop the product in a nebulizer with character-istics that are hard to copy, thereby effectively creating a co-labelled or combination product. Such features can include medication volume and breath-actuation men-tioned above, patient management systems discussed below, or a bespoke interface between the drug packag-ing and device.[39, 40] However, this would then potentially preclude the device from being used with other, general-purpose nebulized products.

Therefore, leaving nebulized product development until late in the drug's lifecycle can make a new drug in nebu-lized form commercially unattractive. In order to over-come this problem, one company, Mylan, has decided to go straight to market with a new long-acting mus-carinic (LAMA) drug in nebulized form, despite having previously licensed a different LAMA for use in inhalers.[41, 42] An alternative novel approach is to focus first on bringing the nebulized formulation to market, and only to start development of a pMDI or DPI once the new drug candidate has successfully demonstrated safety and efficacy. Not only does this mitigate the costs associated with drug failure during development, it also allows outcomes to be evaluated in the most severe group of patients (already requiring nebulized treat-ments), in whom a positive effect should be easiest to demonstrate. This has been modelled from a financial perspective, and shown to be likely to give a much better financial return on research and development invest-ments, even when drug sales are modest.[43] Furthermore, it is generally easier and quicker to develop a formulation which is physically and chemically stable for a nebulizer than for an inhaler, even if this means developing a lyophilized product for reconstitution, fewer challenges to making formulations that are easily dispersible back to respirable form. Consequently, there is more time for the inhaler formulation to be developed while the nebulized variant is already in the clinic.

A new drug may also benefit from a new device. The increasing linkage between drug and delivery device during clinical trials also has added significance beyond the development stage. The microelectronic platform upon which mesh nebulizers are built can easily be supplemented with sensors, logic circuits, antennas and microprocessors during development. These additional features could then be used to provide sophisticated collection, analysis and transmission of data for incorporation into an e-health system for patient management. Data pertaining to nebulizer operation, usage characteristics and a range of measures relevant to monitoring disease progression could then be leveraged to aid the success of the new drug product during clinical studies and approval. The assessment of adherence to drug usage in clinical trials is required by the principles of good clinical practice, and the collection of data such as adherence and compliance is currently incorporated into a range of devices.[44] The expansion into parameters providing information on disease progression is in its infancy.[45] But if the data can be shown to help the patient improve self-management of his or her condition, it can be expected to be seen as an advantage that outweighs concerns around privacy. Beyond launch, these same features could be used to ensure the continued commercial success of the drug, with better disease control promoting continued use of drug and device.

Patients enrolled in clinical studies are not typical of the wider population in terms of their amount of interaction with healthcare providers. One of the fundamental issues affecting the treatment of respiratory diseases remains the issue of poor adherence to prescribed regimen, which can be subdivided into three phases: initiation, implementation and persistence.[46] The prescription of a new drug with a user friendly "aspirational" technology device package could contribute to successful initiation of treatment while an easy-to-use design with feedback features to aid correct use of the device could aid implementation. But aiding persistence may require extended logging, memory and communication modules that are already proving to be advantageous in the treatment of respiratory disease. One example of this technology in use is in the treatment of cystic fibrosis. An e-health system that consists of a mesh nebulizer fitted with a logging function can be used in conjunction with communication hardware and software to allow uploading of adherence information to a secure central server, compliant with all data privacy and security regulations. Patients, clinicians and support personnel such as relatives can log into the server to examine data concerning treatment and adherence. This type of approach has been shown to facilitate: an increase in the number of doses taken correctly,[47] high levels of adherence that can be sustained over 12 months,[48] a reduction in treatment

times[49] and a correlation of better lung function with optimum adherence.[50]

Looking toward the future of nebulized therapy

Nebulized drug therapy is outpacing that of the pMDIs and DPIs, despite a limited number of new drug launches compared to those formulated for inhalers. One example of this is in the development of nebulized therapies for the treatment of common conditions such as COPD. The development of long-acting β-agonist and anti-muscarinics in recent years has been mainly restricted to pMDI and DPI inhaler formulations,[12] leaving a gap in the provision of nebulized drugs for patients discharged from the hospital with a nebulizer. Another example of a potentially missed opportunity is the use of nebulized formulations in the early stages of drug development, followed by a switch to an inhaler once proof-of-principle had been established. Continuing the nebulizer formulation through to launch, in parallel with inhaler development following proof-of-principle may, in many cases, have given a greater return on investment and the potential for superior outcome data in the most severe patients.

Coupled with innovations in mesh technology leading to nebulizers that are more patient-friendly, there are signs of a resurgence of interest in nebulized therapies, recognizing that this is an opportunity that has been overlooked in recent years. In addition, the electronic basis on which mesh nebulizers are built provides the opportunity to integrate e-health functions into modern nebulizers to aid patient self-management in the quest for better disease control. Whereas for inhalers, the inclusion of e-health features represents significant additional cost and complexity, it can fit seamlessly into mesh nebulizers. Such inclusion can provide an opportunity to increase, not only the adherence to prescribed regimen and compliance with correct device use, but also overall control and management of patients, who by their very nature are vulnerable or in poor health and so most likely to benefit from such advances.

References

1. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013; Sep 13; 9:CD000052.

2. Osmond MH, Gazarian M, Henry RL, Clifford TJ, Tetzlaff J. PERC Spacer Study Group. Barriers to metered-dose inhaler/spacer use in Canadian pediatric emergency departments: A national survey. Acad Emerg Med. 2007; Nov;14(11):1106-1113.

3. Yaxley JP. Prescribing patterns of nebulized bronchodilators: A prospective chart review. J Family Med Prim Care. 2016; Apr-Jun;5(2): 501-502.

4. Salzman GA, Steele MT, Pribble JP, Elenbaas RM, Pyszczynski DR. Aerosolized metaproterenol in the treatment of asthmatics with severe airflow obstruction. Comparison of two delivery methods. Chest. 1989;95(5):1017-1020.

5. Fink JB, Colice GL, Hodder R. Inhaler devices for patients with COPD. COPD. 2013;10(4):523-535.

6. MM&M Therapeutic Focus, Top 25 respiratory products, 2014-2015. [Cited Apr 27, 2017] Available at: http://www.mmm-online.com/commercial/top-25-respiratory-products-2014-2015/article/485567/.

7. United Nations Environmental Programme. June 2015 Report of the technology and economic assessment panel, Volume 1. [Cited Apr 27, 2017] Available at: http://ozone.unep.org/en/teap-june-2015-progress-report-volume-1.

8. World Health Organization. Life expectancy increased by 5 years since 2000, but health inequalities persist. [Cited Apr 27, 2017] Available at: http://www.who.int/mediacentre/news/releases/2016/health-inequalities-persist/en/.

9. World Health Organization. Chronic obstructive pulmonary disease (COPD). [Cited Apr 27, 2017] Available at: http://www.who.int/mediacentre/factsheets/fs315/en/.

10. Taffet GE, Donohue JF, Altman PR. Considerations for managing chronic obstructive pulmonary disease in the elderly. Clin Interv Aging. 2014;9:23-30.

11. Winningham RE. Theravance Biopharma. Presented at: 14th Annual Needham Healthcare Conference, New York, NY, US, April 2015. [Cited Feb 20, 2017] Available at: www.sec.gov/Archives/edgar/data/1583107/000110465915027343/a15-9036_1ex99d1.htm.

12. Pritchard JN. Industry guidance for the selection of a delivery system for the development of novel respiratory products. Expert Opin Drug Deliv. 2015;12(11):1755-1765.

13. Welch MJ. Nebulization therapy for asthma: A practical guide for the busy pediatrician. Clin Pediatr. 2008;47(8):744-756.

14. Slator L, Parker J, Hardaker L, Potter R. Assessment of delivered dose rate from 2 mesh nebulizers tested with an adult breathing pattern and 2 drugs. Presented at: Drug Delivery to the Lungs Conference 27, Edinburgh, Scotland, UK, December 7-9, 2016.

15. Hatley RHM, Hardaker LEA, Metcalf AP, Parker J, Quadrelli F, Pritchard JN. Ensuring the consistency of performance of mesh nebulizers. Presented at: Drug Delivery to the Lungs Conference 27, Edinburgh, Scotland, UK, December 7-9, 2016.

16. Hatley RHM, Rowe L, Rabbetts I, Quadrelli F. Optimizing patient experience of nebulizer treatments. Eur Respir J. 2016;48:PA4082.

17. Rottier BL, van Erp CJP, Sluyter TS, Heijerman HGM, Frijlink HW, and de Boer AH. Changes in performance of the pari eFlow rapid and pari LC plus during 6 months use by CF patients. J Aerosol Med Pulm Drug Deliv. 2009;22:1-7.

18. Aerogen pioneering aerosol drug delivery. Clinical white paper. [Cited Apr 27, 2017] Available at: https://www.aerogen.com/products/aerogen-ultra/.

19. Ingram H: Nebulisers—World—2014 . IHS Technology; 2014 [Cited Feb 20, 2017] Available at: https://technology.ihs.com/435839/nebulizers-2014.

20. Degtyareva Y, Metcalf A, Hardaker LEA, Pritchard JN, Hatley, RHM, Efficiency of the Micro mesh nebulizer tested with three different fill volumes. In: Dalby RN, Byron PR, Peart JD, et al. editors. Respiratory Drug Delivery Europe 2015. Davis Healthcare International; River Grove, IL:

2015. p. 401-404.

21. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med. 2005;Dec 15;172(12):1497-1504.

22. Darquenne C. Aerosol deposition in health and disease. J Aerosol Med Pulm Drug Deliv. 2012;25(3):140-147.

23. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. Am J Respir Crit Care Med. 2014;189(8): 975-982.

24. Pritchard JN, von Hollen D, Hatley RHM. The utility of monitoring inhaled drug adherence and technique in clinical trials. In: Dalby RN, Byron PR, Peart JD, et al. editors. Respiratory Drug Delivery Europe 2015. Davis Healthcare International; River Grove, IL: 2015. p. 413-417.

25. ClinicalTrials.gov. Search for Studies. [Cited Apr 27, 2017] Available at: https://clinicaltrials.gov.

26. clinicaltrialsregister.eu. Clinical Trials Search. [Cited Apr 27, 2017] Available at: https://www.clinicaltrialsregister.eu/ctr-search/search.

27. Denyer J, and Dyche T. The Adaptive Aerosol Delivery (AAD) technology: Past, present, and future. J Aerosol Med Pulm Drug Deliv. 2010;23(Suppl 1):S1-S10.

28. Lass JS, Sant A, and Knoch M. New advances in aerosolised drug delivery: Vibrating membrane nebuliser technology. Expert Opin Drug Deliv. 2006;3(5):693-702.

29. Evaluate Ltd. Aerogen and Medical Industries America announce U.S. introduction of Aeroneb Go nebulizer. 2004 [Cited Feb 13, 2017] Available at: http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=71104.

30. Berg EB, and Picard RJ. *In vitro* delivery of budesonide from 30 jet nebulizer/compressor combinations using infant and child breathing patterns. Respir Care. 2009;54(12):1671-1678.

31. Loffert DT, Ikle D, and Nelson HS. A comparison of commercial jet nebulizers. Chest. 1994;106(6):1788-1792.

32. European Committee for Standardization (CEN): EN 13544-1: 2007+A1:2009. Respiratory therapy equipment: Nebulizing systems and their components. European Committee for Standardization; 2010.

33. ISO 27427:2013(E), Anaesthetic and respiratory equipment—Nebulizing systems and components.

34. Hatley RHM, Byrne SM. Variability in delivered dose and respirable delivered dose from nebulizers: Are current regulatory testing guidelines sufficient to produce meaningful information? Med Devices (Auckl) 2017;10:17-28.

35. World Health Organization: Adherence to long-term therapies: Evidence for action. World Health Organization, Geneva, Switzerland, 2003.

36. Mularksi R, McBurnie MA, Donovan JR, Walker KL, Gillespie SE, Vollmer WM. Adherence with inhaled respiratory therapeutics is associated with reduced acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J. 2011;38:(Suppl 55):4868.

37. Bollu V, Ernst FR, Karafilidis J, Rajagopalan K, Robinson SB, Braman SS. Hospital readmissions following initiation of nebulized arformoterol tartrate or nebulized short-acting beta-agonists among inpatients treated for COPD. Int J Chron Obstruct Pulmon Dis. 2013;8: 631-639.

38. Pritchard JN. Rethinking the paradigm for the development of inhaled drugs. Int J Pharm. 2015; 496(2): 1069-1072.

39. Loenner M, Gallem T, Hetzer U, inventors; Pari Pharma GmbH, assignee. Disposable ampoule for an aerosol generating device. United States patent US 9,265,900 (B2). Filed Nov 21 2008; issued Feb 23 2016.

40. Loeffler JP, Poynter RQ, Rapp D, Klimowicz M, inventors; Aerogen Inc, assignee. Fluid filled ampoules and methods for their use in aerosolizers. United States patent US 7,100,600 (B2). Filed Mar 20 2001;issued Sep 5 2006.

41. Theravance Biopharma and Mylan initiate phase 3 program for Revefenacin (TD-4208) for treatment of chronic obstructive pulmonary disease (COPD). [Cited Apr 27, 2017] Available at http://newsroom.mylan.com/2015-09-14-Theravance-Biopharma-and-Mylan-Initiate-Phase-3-Program-for-Revefenacin-TD-4208-for-Treatment-of-Chronic-Obstructive-Pulmonary-Disease-COPD.

42. Mylan announces acquisition of rights to novel LAMA respiratory compound from Pfizer. [Cited Apr 27, 2017] Available at: http://newsroom.mylan.com/press-releases?item=123190.

43. Pritchard JN. Maximizing the effectiveness of the inhaled drug development process. In: Dalby RN, Byron PR, Peart J, et al. editors. Respiratory Drug Delivery 2016. Davis Healthcare International; River Grove, IL: 2016. 497-502.

44. Pritchard JN, Nicholls C. Emerging technologies for electronic monitoring of adherence, inhaler competence, and true adherence. J Aerosol Med Pulm Drug. Deliv. 2015;28(2):69-81.

45. Al Rajeh AM, Hurst JR. Monitoring of physiological parameters to predict exacerbations of chronic obstructive pulmonary disease (COPD): A systematic review. J Clin Med. 2016;Nov 25;5(12).pii:E108.

46. Vrijens B, De Geest S, Huges DA, Przemyslaw K, Demonceau J, Ruppar T, et al, ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73:691-705.

47. Pollard K, Watson R, Conway SP, Etherington C, Ollerton S, Peckham D. The effect of remote monitoring and third party intervention on adherence with inhaled therapies in patients with cystic fibrosis using the I-neb Insight Online patient management system. J Cyst Fibros. 2012;11(Suppl 1):S9.

48. McNamara PS, McCormack P, McDonald AJ, Heaf L, Southern KW. Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. J Cyst Fibros. 2009;8(4):258-263.

49. McCormack P, Southern KW, McNamara PS. New nebulizer technology to monitor adherence and nebulizer performance in cystic fibrosis. J Aerosol Med Pulm Drug Deliv. 2012;25(6):307-309.

50. Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. J Cyst Fibros. 2011;10(4):258-264.

John N. Pritchard, PhD is Director of Project Management and Technology at Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester, West Sussex, PO20 2FT, UK, John.Pritchard@philips.com. Website: http://www.philips.co.uk/healthcare/solutions/sleep-and-respiratory-care/respiratory-drug-delivery.