Does size really matter

Jabbal, Sunny; Poli, Gianluigi; Lipworth, Brian

Published in:
Journal of Allergy and Clinical Immunology

DOI:
10.1016/j.jaci.2016.11.036

Publication date:
2017

Elsevier Editorial System(tm) for Journal of Allergy and Clinical Immunology
Manuscript Draft

Manuscript Number: JACI-D-16-00883R1

Title: Does size really matter- relationship of particle size to lung deposition and exhaled fraction.

Article Type: Letter to the Editor

Section/Category: Asthma and Lower Airway Disease

Keywords: particle size; exhaled fraction; lung deposition; asthma

Corresponding Author: Prof. Brian Lipworth, MD

Corresponding Author's Institution: University of Dundee

First Author: Sunny Jabbal, Mb ChB

Order of Authors: Sunny Jabbal, Mb ChB; Gianluigi Poli, M.Sc; Brian Lipworth, Mb ChB, MD

Manuscript Region of Origin: UNITED KINGDOM

Abstract: Particle size is the major determinant in the deposition and distribution of inhaled drug within the lungs and hence is related to local efficacy. It has been previously thought that however, extra fine particles are mostly exhaled. Our data demonstrates that extra fine particles are not associated with an appreciably higher exhaled fraction.

Does size really matter- relationship of particle size to lung deposition and exhaled fraction.

[1]*Sunny Jabbal Mb ChB,* [2]*Gianluigi Poli MSc,* [1]*Brian Lipworth MD*

[1]*Scottish Centre for Respiratory Research, Ninewells Hospital & Medical School, Dundee UK.*

[2] *Global Clinical Development, Chiesi Farmaceutici S.p.A., Parma, Italy.*

Correspondence to: Dr BJ Lipworth, Scottish Centre for Respiratory Research, Ninewells Hospital & Medical School, University of Dundee, Dundee, DD1 9SY. Tel: +44 1382 383188 b.j.lipworth@dundee.ac.uk

Declaration of funding: Unrestricted grants from Department and from Chiesi

Capsule summary: We demonstrate that extra-fine particles are not associated with an appreciably higher exhaled fraction, hence explaining their efficacy profile in asthma.

Keywords: Particle size, exhaled, lung deposition, asthma

Word Count: 944

Particle size is the major determinant in the deposition and distribution of inhaled drug within the lungs and hence is related to local efficacy . The particle size distribution of an aerosol is usually expressed in terms of its mass median aerodynamic diameter (MMAD). Particles deposit in the respiratory tract by inertial impaction (3-6µm), sedimentation (1-3µm) and diffusion (<1µm). In order to reach the lower respiratory tract past the carina the MMAD of inhaled particles should be less than 5µm in diameter , specifically the particle size with the most efficient deposition in the small airways ,so called extra fine particle fraction is said to be <2um (1) . It has been demonstrated that smaller particles of inhaled salbutamol achieve greater overall lung deposition, along with greater peripheral lung distribution (2). Moreover smaller particles of long acting beta-agonist are also associated with improved small airways responses measured by impulse oscillometry (3).

Whilst it is widely accepted that for efficient lung deposition, the MMAD should be lower than 5µm, it is more controversial what happens to small particles with MMAD lower than 1µm. It conventionally believed that, particles <1 µm are mainly exhaled and therefore may not able to elicit any therapeutic activity within the lungs, due to their extremely low settling velocity. Conversely, it could be argued that although small particles have a greater potential to be exhaled, this is counterpoised by their capability to be distributed throughout the whole lungs and reach the distal airways with a high pulmonary deposition .We have therefore evaluated the relationship between in vitro MMAD and in vivo lung deposition (LD), and the exhaled fraction (EF) expressed as fraction of the delivered dose, using pooled analysis from relevant literature using scintigraphic studies conducted in healthy volunteers and asthmatic patients using pMDI or DPI. Moreover the relationship between the ratio of EF to LD and MMAD was also evaluated.

We used pooled data (supplementary table) from 18 different studies ,comprising 32 separate inhaled formulations , in healthy subjects (n=173) and asthmatics (n=124) ,21 formulations in healthy volunteers, 15 with pressurised metered dose inhalers (pMDI) and 6 with dry powder inhalers (DPI); and 11 formulations in asthmatic patients, 8 with pMDI and 3 with DPI were evaluated. All participants were aged 18-65, and asthmatic patients had a mean FEV_1 of 85% predicted, we combined the data in asthma patients with that of healthy volunteers. All subjects were non smokers .

Lung deposition increased in relation to decreased MMAD, such that when the MMAD was around 1 µm the lung deposition exceeded 50% of the delivered dose and became markedly lower when MMAD approaches 4 µm (Figure 1a). Pointedly this pattern was similar in healthy and asthmatic patients. The exhaled fraction remained low irrespective of particle size. The mean amount of particles exhaled amounted to approximately 5 % of the emitted dose thus demonstrating that such extra fine particles are suitable for inhalation. Furthermore, the ratio of the amount exhaled to the amount deposited in the lung was found to be independent from the MMAD (Figure 1b).

Our findings are consistent with previous data with inhaled salbutamol which similarly demonstrated that total lung deposition was greatest in particles with a MMAD of 1.5µm compared to particles of 3µm and 6µm (4). It could be argued that the ability to correctly perform the inhalation including an adequate breath-holding is likely to decrease the amount of exhaled drug. In this regard in all of the included studies in our cohort , inhaler technique with a given device was standardised .Previous data(5) have demonstrated that extra-fine particles are able to reach the small airways more effectively and hence achieve better drug distribution throughout the whole bronchial tree. Interestingly they also indicate that the exhaled fraction is approximately 12 % of the dose deposited in the lung and is totally independent from the MMAD further confirming that extra-fine particles are suitable for inhalation. The clinical relevance of extra-fine particles <2um has been demonstrated by Nicolini and colleagues (6) who compared extra-fine (MMAD 1.1um) versus coarse particle HFA-beclometasone (MMAD 3.5um) , in individuals with asthma, and demonstrated the extra-fine particles significantly reduced both bronchial and alveolar exhaled nitric oxide unlike coarse particle, which only reduced bronchial exhaled nitric oxide. Moreover, extra-fine HFA-flunisolide (MMAD 1.2um) has been shown to reduce histological evidence of eosinophilic and interleukin 5 mediated inflammation in peripheral and central airways after 6 weeks of treatment (7). If these extra-fine particles were mostly exhaled, as conventionally believed, one would not expect there to be an improvement in small airway inflammation as evidenced invasively and non-invasively. It should be appreciated that there will be a normal distribution of particle size around the MD ,such with an MMAD of 1.1um there will be a proportion of particles <1um. In this regard such smaller particles may be absorbed from the alveoli and potentially increase systemic adverse effects , although such alveolar deposition might also contribute to anti-asthmatic efficacy as shown in association with the nocturnal phenotype (8). Our asthma cohort of asthma patients had an FEV1 of 85% predicted, in this regard it has been shown that there is evidence of small airways dysfunction in terms of a raised peripheral airways resistance occurring in approximately of half of patients who have a preserved FEV1 >80% predicted (9).

In summary the present data demonstrate that the EF/LD ratio is independent from the MMAD, suggesting that extra-fine particles will not be associated with an appreciably higher exhaled fraction. Further prospective studies are required to assess how this relates to clinical efficacy in patients with more severe asthma, perhaps using impulse oscillometry to better assesses the small airways (10).

References:

1.Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. Lancet Respir Med. 2014;2(6):497-506

2.Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. J Appl Physiol. 2003;95(5):2106-12.

3.Manoharan A, von Wilamowitz-Moellendorff A, Morrison A, Lipworth BJ. Effects of formoterol or salmeterol on impulse oscillometry in patients with persistent asthma. J Allergy Clin Immunol. 2016;137(3):727-33 e1.

4 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;172(12):1497-504.

5. De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, et al. Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. J Aerosol Med Pulm Drug Deliv. 2010;23(3):137-48.(2)

6. Nicolini G, Chetta A, Simonazzi A, Tzani P, Aiello M, Olivieri D. Both bronchial and alveolar exhaled nitric oxide are reduced with extrafine beclomethasone dipropionate in asthma. Allergy Asthma Proc. 2010;31(5):85-90.
7. Hauber HP, Gotfried M, Newman K, Danda R, Servi RJ, Christodoulopoulos P, et al. Effect of HFA-flunisolide on peripheral lung inflammation in asthma. J Allergy Clin Immunol. 2003;112(1):58-63.
8 . Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med. 1996;154(5):1505-10.
9 Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. Eur Respir J. 2014;44(5):1353-5.
10. Jabbal S, Manoharan A, Lipworth J, Lipworth B. Utility of impulse oscillometry in patients with moderate to severe persistent asthma. J Allergy Clin Immunol. 2016;138(2):601-3.

Figure No.1 - Marked

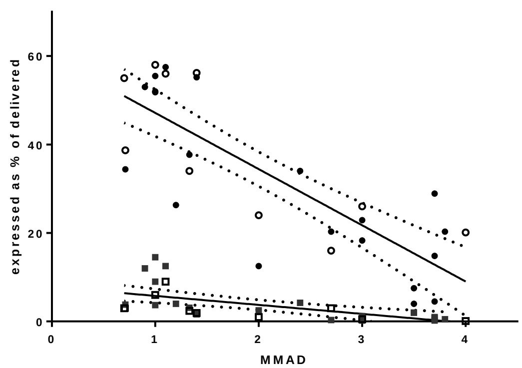
Does size really matter- relationship of particles size to lung deposition and exhaled fraction.

Figure 1.a

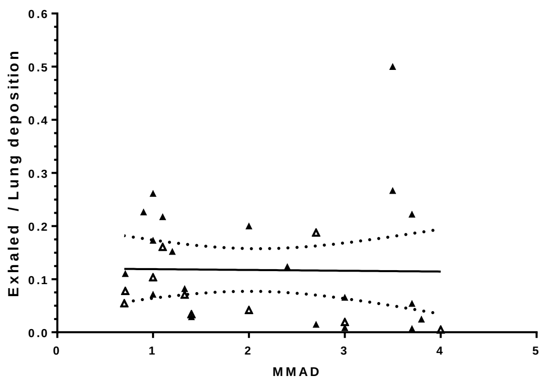
Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (µm). Regression line and the 95% confidence intervals are also shown.

Figure 1.a

Pooled data from 18 different studies, comprising 32 separate inhaled formulations, each point represents a particular formulation. Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (µm). Regression line and the 95% confidence intervals are also shown.



Full squares and circles: healthy volunteers
Open squares and circles: asthmatic patients



Full triangles: healthy volunteers
Open triangles: asthmatic patients

Figure 1.b
Ratio of Exhaled vs lung deposited drug as function of MMAD (µm). Regression line and the 95% confidence intervals are also shown.

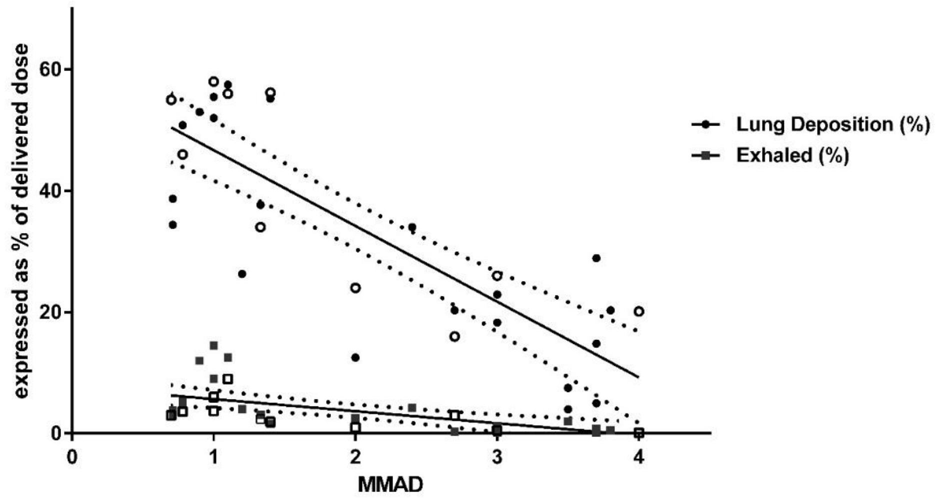
Formatted: Justified, Line spacing: 1.5 lines

Figure No 1. - Unmarked

Click here to download Figure No. - Unmarked: Figure 1 JACI clean.docx

Figure 1.a

Pooled data from 18 different studies, comprising 32 separate inhaled formulations, each point represents a particular formulation. Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (µm). Regression line and the 95% confidence intervals are also shown.



Healthy volunteers: Full squares, circle and triangle

Asthmatic patients: Open squares, circles and triangles

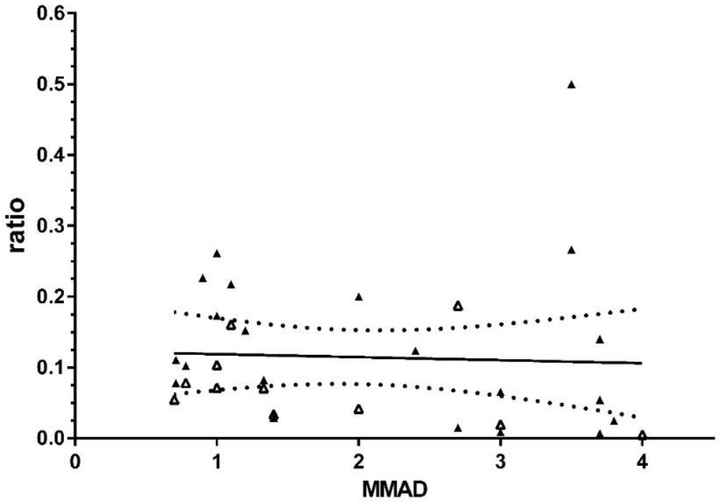


Figure 1.b

Ratio of Exhaled vs lung deposited drug as function of MMAD (µm). Regression line and the 95% confidence intervals are also shown.

Supplementary Table 1:

Source data

Häussermann S, Acerbi D, Brand P, ~~Hederer B, Austen~~Herpich C, Poli G, ~~Dewberry H~~Sommerer K, Meyer T. ~~Higher lung~~Lung deposition ~~with Respimat® Soft MistTM Inhaler than~~of formoterol HFA~~-MDI~~ (Atimos/Forair) in healthy volunteers, asthmatic and COPD patients~~ with poor technique. International Journal of Chronic Obstructive Pulmonary Disease. 2008;~~. J Aerosol Med. 2007 Fall;20(3~~(4):763-770~~):331-41.	
Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone : a cross-over study in healthy volunteers. Chest. 2002 Aug;122(2):510-6. PubMed PMID: 12171824.	
Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. Eur Respir J. 1998 Dec;12(6):1346-53. PubMed PMID: 9877489.	
Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. J Aerosol Med. 2001 Summer;14(2):197-208. PubMed PMID: 11681651.	
De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, Sommerer K, Meyer T, Mariotti F. Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. J Aerosol Med Pulm Drug Deliv. 2010 Jun;23(3):137-48. doi: 10.1089/jamp.2009.0772. PubMed PMID: 20109122; PubMed Central PMCID: PMC3123836.	
Leach CL, Colice GL. A pilot study to assess lung deposition of HFA-beclomethasone and CFC-beclomethasone from a pressurized metered dose inhaler with and without add-on spacers and using varying breathhold times. J Aerosol Med Pulm Drug Deliv. 2010 Dec;23(6):355-61. doi: 10.1089/jamp.2009.0783. Epub 2010 Jun 24. PubMed PMID: 20575669.	
Pickering H, Pitcairn GR, Hirst PH, Bacon PR, Newman SP, Affrime MB, Marino M. Regional lung deposition of a technetium 99m-labeled formulation of mometasone furoate administered by hydrofluoroalkane 227 metered-dose inhaler. Clin Ther. 2000 Dec;22(12):1483-93. PubMed PMID: 11192139.	
Leach CL, Bethke TD, Boudreau RJ, Hasselquist BE, Drollmann A, Davidson P, Wurst W. Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. J Aerosol Med. 2006 Summer;19(2):117-26. PubMed PMID: 16796536.	
Warren S, Taylor G, Smith J, Buck H, Parry-Billings M. Gamma scintigraphic evaluation of a novel budesonide dry powder inhaler using a validated radiolabeling technique. J Aerosol Med. 2002 Spring;15(1):15-25. PubMed PMID: 12006142.	

Formatted: Left, Line spacing: Multiple 1.08 li

Inserted Cells

Formatted Table

Formatted: English (United Kingdom), Highlight

Formatted: English (United Kingdom), Highlight

Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, Hermann R. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. Eur Respir J. 2000 Jul;16(1):178-83. PubMed PMID: 10933104.	
Newman SP, Pitcairn GR, Adkin DA, Vidgren MT, Silvasti M. Comparison of beclomethasone dipropionate delivery by easyhaler dry powder inhaler and pMDI plus large volume spacer. J Aerosol Med. 2001 Summer;14(2):217-25. PubMed PMID: 11681653.	
Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. Respir Med. 2006 Mar;100(3):375-84. Epub 2005 Nov 4. PubMed PMID: 16275052.	
Hirst PH, Bacon RE, Pitcairn GR, Silvasti M, Newman SP. A comparison of the lung deposition of budesonide from Easyhaler, Turbuhaler and pMDI plus spacer in asthmatic patients. Respir Med. 2001 Sep;95(9):720-7. PubMed PMID: 11575892.	
Leach CL, Kuehl PJ, Chand R, Ketai L, Norenberg JP, McDonald JD. Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients. Ann Allergy Asthma Immunol. 2012 Mar;108(3):195-200. doi: 10.1016/j.anai.2012.01.010. PubMed PMID: 22374204.	
Leach CL, Kuehl PJ, Chand R, McDonald JD. Respiratory Tract Deposition of HFA-Beclomethasone and HFA-Fluticasone in Asthmatic Patients. J Aerosol Med Pulm Drug Deliv. 2016 Apr;29(2):127-33. doi: 10.1089/jamp.2014.1199. Epub 2015 Jun 10. PubMed PMID: 26061801.	
Newman SP, Sutton DJ, Segarra R, Lamarca R, de Miquel G. Lung deposition of aclidinium bromide from Genuair, a multidose dry powder inhaler. Respiration. 2009;78(3):322-8. doi: 10.1159/000219676. Epub 2009 May 16. PubMed PMID: 19451700.	
Unpublished data: Chiesi Clinical Study CHF4226 HFA MDI 19.10.2006 ~~Chiesi001 Formoterol 19.10.2006~~Chiesi Report CCD0815CSR0036	

Supplementary Table 1:

Source data

Häussermann S, Acerbi D, Brand P, Herpich C, Poli G, Sommerer K, Meyer T. Lung deposition of formoterol HFA (Atimos/Forair) in healthy volunteers, asthmatic and COPD patients. J Aerosol Med. 2007 Fall;20(3):331-41.	
Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone : a cross-over study in healthy volunteers. Chest. 2002 Aug;122(2):510-6. PubMed PMID: 12171824.	
Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. Eur Respir J. 1998 Dec;12(6):1346-53. PubMed PMID: 9877489.	
Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. J Aerosol Med. 2001 Summer;14(2):197-208. PubMed PMID: 11681651.	
De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, Sommerer K, Meyer T, Mariotti F. Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. J Aerosol Med Pulm Drug Deliv. 2010 Jun;23(3):137-48. doi: 10.1089/jamp.2009.0772. PubMed PMID: 20109122; PubMed Central PMCID: PMC3123836.	
Leach CL, Colice GL. A pilot study to assess lung deposition of HFA-beclomethasone and CFC-beclomethasone from a pressurized metered dose inhaler with and without add-on spacers and using varying breathhold times. J Aerosol Med Pulm Drug Deliv. 2010 Dec;23(6):355-61. doi: 10.1089/jamp.2009.0783. Epub 2010 Jun 24. PubMed PMID: 20575669.	
Pickering H, Pitcairn GR, Hirst PH, Bacon PR, Newman SP, Affrime MB, Marino M. Regional lung deposition of a technetium 99m-labeled formulation of mometasone furoate administered by hydrofluoroalkane 227 metered-dose inhaler. Clin Ther. 2000 Dec;22(12):1483-93. PubMed PMID: 11192139.	
Leach CL, Bethke TD, Boudreau RJ, Hasselquist BE, Drollmann A, Davidson P, Wurst W. Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. J Aerosol Med. 2006 Summer;19(2):117-26. PubMed PMID: 16796536.	
Warren S, Taylor G, Smith J, Buck H, Parry-Billings M. Gamma scintigraphic evaluation of a novel budesonide dry powder inhaler using a validated radiolabeling technique. J Aerosol Med. 2002 Spring;15(1):15-25. PubMed PMID: 12006142.	

Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, Hermann R. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. Eur Respir J. 2000 Jul;16(1):178-83. PubMed PMID: 10933104.	
Newman SP, Pitcairn GR, Adkin DA, Vidgren MT, Silvasti M. Comparison of beclomethasone dipropionate delivery by easyhaler dry powder inhaler and pMDI plus large volume spacer. J Aerosol Med. 2001 Summer;14(2):217-25. PubMed PMID: 11681653.	
Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. Respir Med. 2006 Mar;100(3):375-84. Epub 2005 Nov 4. PubMed PMID: 16275052.	
Hirst PH, Bacon RE, Pitcairn GR, Silvasti M, Newman SP. A comparison of the lung deposition of budesonide from Easyhaler, Turbuhaler and pMDI plus spacer in asthmatic patients. Respir Med. 2001 Sep;95(9):720-7. PubMed PMID: 11575892.	
Leach CL, Kuehl PJ, Chand R, Ketai L, Norenberg JP, McDonald JD. Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients. Ann Allergy Asthma Immunol. 2012 Mar;108(3):195-200. doi: 10.1016/j.anai.2012.01.010. PubMed PMID: 22374204.	
Leach CL, Kuehl PJ, Chand R, McDonald JD. Respiratory Tract Deposition of HFA-Beclomethasone and HFA-Fluticasone in Asthmatic Patients. J Aerosol Med Pulm Drug Deliv. 2016 Apr;29(2):127-33. doi: 10.1089/jamp.2014.1199. Epub 2015 Jun 10. PubMed PMID: 26061801.	
Newman SP, Sutton DJ, Segarra R, Lamarca R, de Miquel G. Lung deposition of aclidinium bromide from Genuair, a multidose dry powder inhaler. Respiration. 2009;78(3):322-8. doi: 10.1159/000219676. Epub 2009 May 16. PubMed PMID: 19451700.	
Unpublished data: Chiesi Clinical Study CHF4226 HFA MDI 19.10.2006 Chiesi Report CCD0815CSR0036	