In Vivo Lung Deposition Feasibility Study Comparing the Respira® Dry Powder Inhaler to the Handihaler® in Human Subjects

Aileen M. Gibbons,[1] Kirby L. Zeman,[2] William D. Bennett,[2] Jacques Pappo,[1] Hugh D.C. Smyth,[3] and Martin J. Donovan[1]

[1]Respira Therapeutics Inc., Austin, TX,USA

[2]Centre for Environmental Medicine & Lung Biology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3]College of Pharmacy, Division of Pharmaceutics, University of Texas at Austin, Austin,TX, USA

KEYWORDS: *in vivo*, gamma scintigraphy, dry powder inhaler (DPI), albuterol sulfate (ALB), novel carrier, Respira®

INTRODUCTION

While there are several dry powder inhalers (DPIs) on the market and several more DPIs in development, there is typically a tradeoff between developing an inexpensive 'passive' device, or a more costly 'active' device that improves dispersion performance. The ideal device remains one that can be used by most patient groups irrespective of lung disease state, delivering high efficiency, combining the flow-rate independence of an active DPI device, with the simplicity and low cost design of a passive DPI. No one inhaler on the market, to date, meets all of the above criteria. Respira Therapeutics® DPI products may represent a first-in-class technology to achieve these goals (1-4). The Respira® inhaler is a passive dry powder device, which utilizes the inhalation energy of the patient, transferring this energy into detaching and deaggregating micronized drug particles. This device has been shown to achieve fine particle fractions in excess of 80% across several drug classes (5). It has also been shown to be largely flow-rate independent (1-4) and, due to its simple and original design, delivers the pure drug particulates without the need for lactose carriers or costly electronic drivers.

The technology employed by the Respira device is uncomplicated and consists simply of a millimeter-sized bead coated with pure micronized drug powder. The mechanism by which this technology achieves a large transfer of inhalation energy into the micronized powder has been presented previously (1-4). Briefly, the balance between strong adhesive forces that diminish

dispersion, and the detachment forces that result in dispersion, is highly dependent on carrier particle size. Because detachment forces increase much faster than adhesive forces as a function of increasing carrier particle size, the balance can be dramatically shifted in favor of dispersion when using millimeter-sized beads. The efficiency of the dispersion engine of the Respira technology is therefore capable of producing %FPFs > 80% for common therapeutic agents for local lung activity (5).

In this current *in vivo* technical feasibility study, our aim was to compare the Respira technology to a leading marketed inhaler via blinded scintigraphy lung deposition imaging. Notably, the Respira technology was not optimized for performance, but rather designed to enable appropriate blinding. Therefore, a head-to-head with the Spiriva Handihaler®, versus the Respira bead technology was achieved (Figure 1).

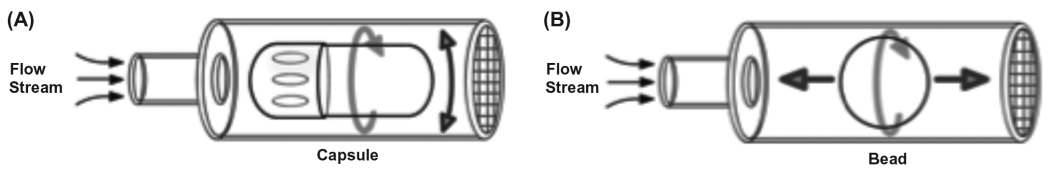

Figure 1. Illustration depicting the relative motions of: (A) a gelatin capsule; and (B) a Respira® bead (Respira technology), which occur within the Handihale® cartridge upon inhalation.

MATERIALS

Albuterol sulfate (ALB) powder was radiolabeled with technetium (^{99m}Tc) (6). In order to validate the labeling technique, linearity of deposition of radiolabeled ALB with ^{99m}Tc radiolabel was assessed using a Next Generation Impactor (NGI) at 45L/min (4kPa pressure drop) (7).

To investigate the initial feasibility and correlation between *in vitro* and *in vivo* data, the regional deposition of inhaled radiolabeled ALB from Respira's technology was compared to the traditional lactose blend of radiolabeled ALB (1% w/w) from the Handihaler device in a single healthy subject (the Handihaler was FDA approved in 2004 for delivery of tiotropium bromide powder to the lungs). The subject was blinded to the devices as the Respira technology was designed to look identical to the Handihaler in external appearance. A single dose was inhaled (ALB; 150-200μg labeled with ^{99m}Tc) on separate randomized study days from either device, Respira Technology or Handihaler. The subject was first trained on the use of the Handihaler device, and by feedback from a flow display (generated from a pneumotach attached to the input of the device), was instructed to target an inhaled flow rate of 45L/min, followed by a breath holding pause of 10 seconds. The subject then exhaled onto a filter to trap any exhaled radioactivity. The peak inspiratory flow-rate and inhaled volume achieved during inhalation of the test aerosols was also recorded for reference. A cobalt 57 transmission scan was performed on the subject prior to inhalation to define their lung borders. Immediately after dosing, posterior planar images of the head and torso were taken using a gamma camera. The doses of radioactivity inhaled from the Respira and the Handihaler devices were kept constant, any disparity between devices was accounted for through normalization of the results to the same median count. Deposited counts in the head, lung, and stomach were also corrected for tissue attenuation, as appropriate, and percentage doses remaining in the device, deposited in the lungs, oropharynx, and exhaled air were quantified.

RESULTS AND DISCUSSION

In vitro validation of the radiolabeling technique was demonstrated by the codeposition of radiolabeled ALB with ^{99m}Tc radiolabel across the NGI stages at 45L/min (Figure 2). A high coefficient of correlation for both devices (Handihaler r^2 = 0.88; Respira r^2 = 0.96) indicated a strong linear association of radiolabeled drug with radiolabel. Previously documented *in vitro* fine particle fraction (%FPF; fine particle dose as a percentage of emitted dose) data for the Handihaler device of 23-25% FPF (8) matched the values obtained in our study of 21 ±4% FPF at an equivalent flow rate.

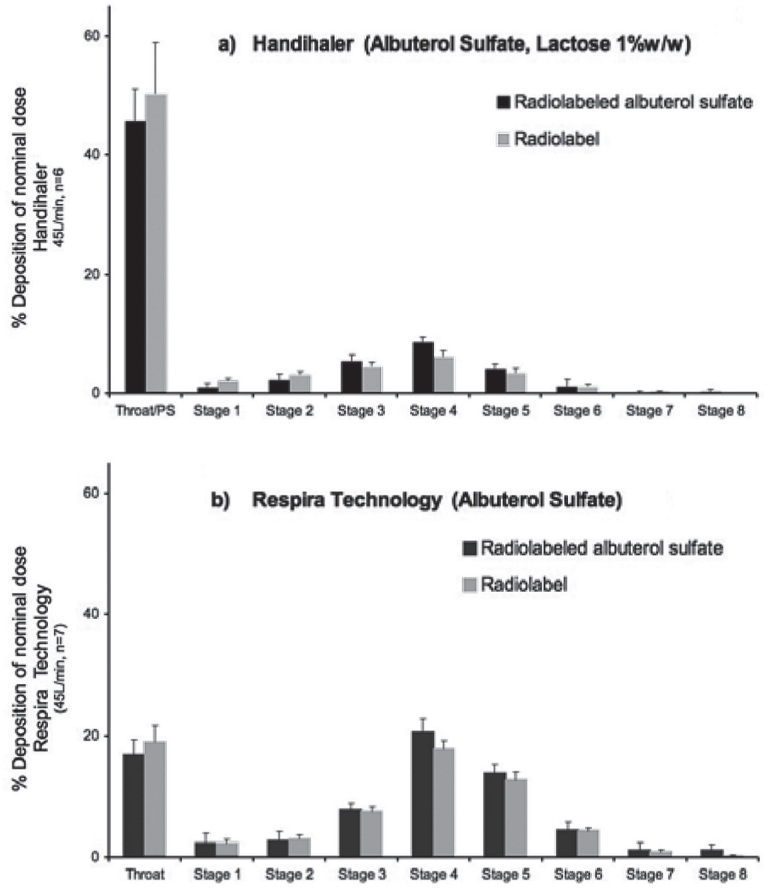

Figure 2. ***In vitro*** **validation of the radiolabeling process: NGI deposition profiles from a) Handihaler® and b) Respira® of ^{99m}Tc radiolabeled ALB powder from both inhalers were assayed by UV (at 230nm) and gamma radiation (counts/second).**

In vivo scintigraphy scans demonstrated the superiority of the Respira technology in delivering ALB to the lungs in this single subject, as can be seen from Figure 3. Respira technology successfully targeted ALB particles to the lungs, delivering 49% of the nominal dose. The Handihaler device performed as expected of a capsule-based lactose formulation with 18% lung deposition (9). High extrathoracic deposition (68% of nominal dose) and concomitant high drug levels in the stomach, detected seconds post inhalation were also observed for the Handihaler device (as indicated in Figure 3).

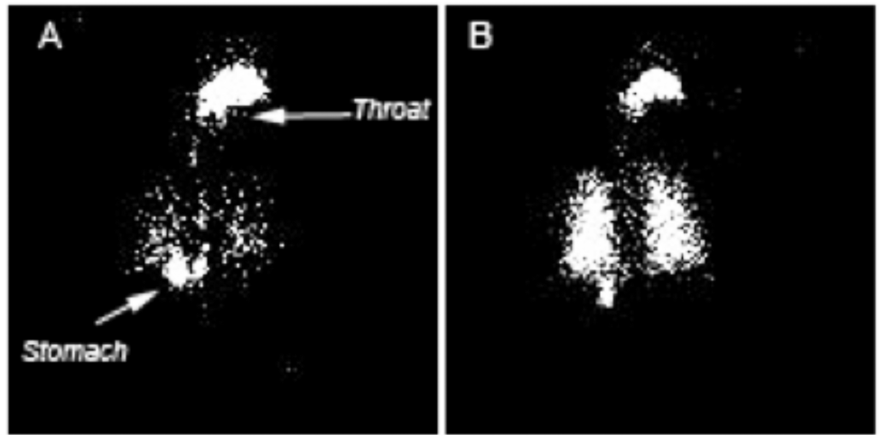

Figure 3: **^{99m}Tc planar scintigraphy depicting the deposition pattern of the radiolabeled drug, albuterol sulfate (ALB), aerosolized from two DPI devices composed of: (A) Handihaler with capsule containing the radiolabeled ALB lactose blend (1%w/w); and (B) Respira technology with pure radiolabeled ALB. Both images were normalized to the same median count.**

CONCLUSIONS

This *in vivo* scintigraphy study demonstrated the superior performance of the Respira technology in delivering larger fractions of drug to the lungs and minimizing extrathoracic deposition compared to a leading commercial DPI, the Handihaler. This was despite the fact that in this study, the Respira technology was not optimized for performance.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of Jihong Wu and Heather Duckworth (Centre for Environmental Medicine & Lung Biology, UNC), and NOVA Chemicals for their supply of bead materials. This study was funded by Respira Therapeutics Inc.

REFERENCES

1. Donovan, M.J. and Gibbons, A. (2011), "Aerosol performance of large drug-coated beads across multiple inhalation flow rates," *AAPS*, Volume #?, Pages?, Washington DC, is this a meeting?

2. Donovan MJ, Gibbons A (2011), "Novel Dual-Chamber Dry Powder Inhaler for Combination Therapy", *AAPS*, Volume #?, Pages?, Washington DC, is this a meeting?

3. Donovan, M.J., Selvam, P., Singh, S., McNair, D., Truman, R., and Smyth, H.D.C. (2009), "Tunable dry powder inhalers: Future or folly?" RDD Europe 2009, R.N. Dalby, P.R. Byron, J. Peart, J.D. Suman, and P.M. Young (eds), Davis Healthcare International Publishing, River Grove, IL, Vol 1, pp. 189-200.

4. Donovan, M.J. and Smyth, H.D.C. (2010), "Widening the lens: Re-evaluating the influence of size and morphology of DPI carrier particle performance," Volume #?, Pages? DDL, Edinburgh, Scotland.

5. Donovan, M.J., Gibbons, A., Pappo, J., and Smyth, H.D.C. (2012), "Novel low resistance DPI for high efficiency delivery in a broad range of drug classes," Respiratory Drug Delivery 2012, Dalby, R.N., Byron, P.R., Peart, J., Farr, S., Suman, J., and Young, P. (eds), Davis Healthcare International Publishing, River Grove, IL, Vol X, pp. XXX-XX (will be added after pagination is complete).

6. Pitcairn, G., Lunghetti, G., Ventura, P., and Newman, S. (1994), "A comparison of the lung deposition of salbutamol inhaled from a new dry powder inhaler, at two inhaled flow rates," *International Journal of Pharmaceutics*, 102(1-3), pp. 11-18.

7. Dolovich, M. (1996), "*In vitro* measurements of delivery of medications from MDIs and spacer devices," *Journal of Aerosol Medicine,* 9, pp. S49-S58.

8. Chodosh, S., Flanders, J.S., Kesten, S., Serby, C.W., Hochrainer, D., and Witek, T.J. (2001), "Effective delivery of particles with the HandiHaler® Dry Powder Inhalation System over a range of chronic obstructive pulmonary disease severity," *Journal of Aerosol Medicine,* 14, pp. 309-15.

9. Brand, P., Meyer, T., Weuthen, T., *et al.* (2007), "Lung deposition of radiolabeled tiotropium in healthy subjects and patients with chronic obstructive pulmonary disease," *The Journal of Clinical Pharmacology,* 47(10), pp. 1335-41.