

# A new tool for inhalers' use and adherence monitoring: the Amiko® validation trial

Braido F<sup>1</sup>, Paa F<sup>2</sup>, Ponti L<sup>3</sup>, Canonica GW<sup>4</sup>

<sup>1,4</sup>Respiratory Diseases and Allergy – Department of Internal Medicine (DIMI) – Azienda Ospedaliera Universitaria San Martino. Genova, Italy.

<sup>2,3</sup>R&D Department - Amiko Srl. Milan, Italy.

**Corresponding Author:**

**Name:** Fulvio Braido

**Email:** fulvio.braido@unige.it

Respiratory Diseases and Allergy – Department of Internal Medicine (DIMI) – Azienda Ospedaliera Universitaria San Martino. Genova, Italy.

**Abstract**— *The lack of adherence to treatment and misuse of inhaled medication are hot topics in asthma and COPD management. Novel electronic monitoring devices are regarded as promising in assessing medication use. The aim of this study was the experimental performance evaluation of an electronic monitoring device (Amiko®) on Ellipta® (GlaxoSmithKline), Spiromax® (Teva Pharmaceutical Industries), and NEXThaler® (Chiesi Farmaceutici). Amiko® introduces a clinically negligible inspiratory flow resistance when added to the tested DPI. It was able to detect the performed inhalation in more than 99% of cases providing also an estimate of the patient's inspiratory effort with a limited gap across the different devices. All the loading manoeuvres were recorded correctly for each DPI, independently of the orientation of the device, resulting in an accuracy of 100.0%. Similarly, the tool was able to detect the device orientation during the performed inhalation with a mean absolute error inferior than 3.53° for the three DPIs. All the above reported results suggest that Amiko® technology will allow to identify, store and communicate relevant data for adherence improvement and misuse correction. Usability test, efficacy and effectiveness in improving respiratory disease management, need to be explored in clinical research setting and in real life.*

**Keywords**— *inhaled device, loading, recording, orientation, inspiratory effort.*

## I. INTRODUCTION

Asthma and COPD are the most common chronic respiratory diseases and represent a great burden for both patients and society (1). In real life, the outcomes of their management are often far from the results obtained in clinical research (2, 3). The reasons could be found both in the substantial differences in comorbidities between patients in traditional RCTs and routine clinical practice, and in the lack of adherence or misuse of the prescribed long-term treatment (6, 7). Suboptimal usage of inhaled medication is one of the main factors responsible for failure to achieve treatment-related goals, and carries a significant economic burden as a result of health care service utilization and overall health care costs. In fact, poor medication-taking behaviour has been associated with an increased risk of hospital admission, increased mortality rate, reduced quality of life, and increased healthcare expenditures (8-10). Interventions to improve medication-taking behaviour, and hence both clinical and economic outcomes, depend upon reliable information about the real-life usage of inhaled medication, and require a genuine understanding of the determinants of suboptimal adherence and poor administration technique (11). Novel electronic monitoring devices are regarded as promising in assessing medication use because of their objectivity and their ability to provide detailed information about actual patterns of medication use in both research and real life settings (12-16). Such information can be helpful for better understanding the use and the effectiveness of an inhaled drug therapy, and for the development and assessment of interventions promoting adherence and correct inhaler technique (17,18). Amiko® (Amiko, Milan, Italy), is an accessory device intended for single-patient use to assist patients and healthcare professionals in recording and monitoring inhaler usage. The device has been developed as an add-on to existing inhalers without any need of intervention on the functionality of the inhaler itself. Amiko® combines sensor technology with proprietary machine learning algorithms to record events such as the inhaler dose loading and the inhalation maneuver, and to capture data about the patient's inspiratory effort and the inhaler orientation during the inhalation. The device stores the data and wirelessly exchanges it with a paired smartphone or a PC. Amiko® is compatible with the associated software application, Quantified Medicine, which provides reports on adherence patterns and inhaler technique.

## II. AIM OF THE STUDY

The aim of this study was to assess the performance of Amiko<sup>®</sup> as an electronic monitoring device for the recording of inhaler usage, on a range of dry powder inhalers (DPI): Ellipta<sup>®</sup> (GlaxoSmithKline), Spiromax<sup>®</sup> (Teva Pharmaceutical Industries), and NEXThaler<sup>®</sup> (Chiesi Farmaceutici).

## III. MATERIALS AND METHODS

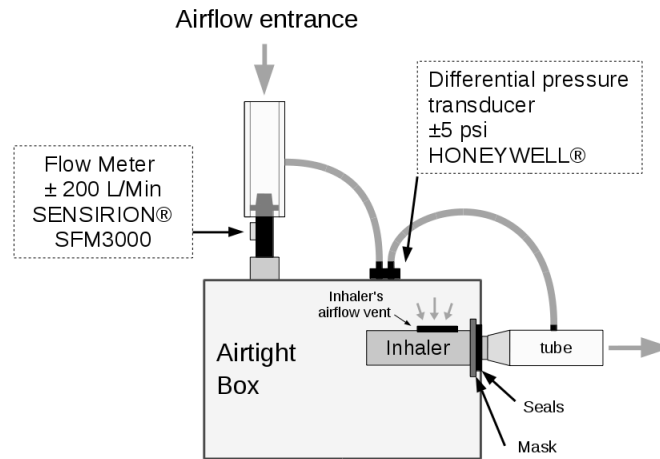
Twelve non-rechargeable Amiko<sup>®</sup> electronic monitors were used with a total of 24 Ellipta<sup>®</sup>, 6 Spiromax<sup>®</sup> and 6 NEXThaler<sup>®</sup> placebo dry powder inhalers, in a performance test period of 3 days (Fig. 1). The number of Ellipta<sup>®</sup> tested was four times higher, as the inhaler contains only one fourth of the total number of doses in NEXThaler<sup>®</sup> and Spiromax<sup>®</sup> (30 versus 120 doses each), and datasets of equal size for each of the feature tested were collected. All procedures and measurements in this study occurred in a dedicated office area at the Amiko R&D Labs in Milan under standardised conditions and were performed by the investigators named above, all of whom had training in correct inhaler technique. Three experimental setups were developed on the basis of the available literature (19-25).



**FIG. 1 THREE DPIs WITH AND WITHOUT AMIKO, FROM LEFT TO RIGHT: ELLIPTA<sup>®</sup>, NEXTHALER<sup>®</sup> AND SPIROMAX<sup>®</sup>. AMIKO<sup>®</sup> HAS BEEN DESIGNED TO FIT ON THE INHALERS WITHOUT ANY NEED OF INTERVENTION ON THE NORMAL**

### 3.1 Setup A – Impact on inspiratory flow resistance

The airflow resistance of the three inhalers with Amiko<sup>®</sup> was measured and compared with the resistance of the inhalers alone, in order to evaluate if Amiko<sup>®</sup> impacts on the inspiratory flow resistance for the inhalers considered. To do so, the inhalers with and without Amiko<sup>®</sup> were placed in an airtight container with a volumetric flow-meter and a differential pressure sensor connected to a sampling tube, in order to measure the flow through and the pressure drop across the inhaler (Fig. 2). An air vacuum was used to generate flow rates in steps of 10 L/Min from 30 L/Min to 90 L/Min. Ten measurements were performed at each step for a total of 70 acquisitions. The pressure drop was recorded at each set flow rate. The resistance for each configuration was then computed according to the formulation proposed in the paper of Clark et al. (25) with the equation  $R = \sqrt{P/F}$ , in which  $P$  is the pressure drop expressed in kPa,  $F$  is the flow in L/Min and  $R$  is the airflow resistance (measured in  $\text{kPa}^{0.5} / (\text{L/Min})$ ). Flow rate and the square root of pressure in DPI are in a linear relationship and the slope of this line is the resistance. The resistance of each inhaler with and without Amiko<sup>®</sup> was then compared to assess whether the Amiko<sup>®</sup> sensors affected the inspiratory flow resistance of Ellipta<sup>®</sup>, Spiromax<sup>®</sup> and NEXThaler<sup>®</sup>.



**FIG. 2 SCHEME OF THE EXPERIMENTAL SETUP EMPLOYED TO ESTIMATE THE IMPACT OF AMIKO® ON THE INSPIRATORY FLOW RESISTANCE OF THE INHALERS. THE PRESSURE SENSOR USED IS A DIFFERENTIAL PRESSURE TRANSDUCER (HONEYWELL, SCC SERIES), 14-BIT RESOLUTION, 500 HZ SAMPLE RATE, WITH A RANGE OF +/- 5 PSI (+/- 34,5 kPa). THE FLOW SENSOR IS A DIGITAL BIDIRECTIONAL FLOW-METER BY SENSIRION (MODEL SFM3000) WITH 14-BIT RESOLUTION AND 500 HZ SAMPLE RATE, WITH A FLOW RANGE OF +/- 200 L/MIN.**

### 3.2 Setup B – Inhalation maneuver detection and inspiratory flow measurement

To test whether Amiko® could detect the inhalation maneuver and provide an estimate of the patient's inspiratory effort, a differential pressure sensor connected to a sampling tube was utilized. This was attached to each of the inhalers' mouthpieces, and was used to measure the inhalation flow rate through the inhaler during inhalations (Fig. 3). Firstly, this setup was employed to determine Amiko®'s performance in detecting a patient's inhalation, over the typical inhalation rates at which these inhalers' performances are tested, up to 90 L/Min (20, 23, 22). Secondly, it was used to measure key parameters of the inhalation profile and compare them with the ones estimated by the Amiko® devices. The inspiratory flow was reconstructed through the value of the pressure measured and the known resistance of the inhaler, according to the equation  $F = \sqrt{P/R}$  where the resistance used for Ellipta® was  $2.86 \cdot 10^{-2} \text{ kPa}^{0.5}/(\text{L}/\text{Min})$  (20), for NEXThaler® was  $3.60 \cdot 10^{-2} \text{ kPa}^{0.5}/(\text{L}/\text{Min})$  (23) and for Spiromax® was  $3.13 \cdot 10^{-2} \text{ kPa}^{0.5}/(\text{L}/\text{Min})$  (22).



**FIG.3 EXPERIMENTAL SETUP WITH DETAIL ON THE SAMPLING TUBE FIXED ON AMIKO®, (LEFT TO RIGHT) FOR ELLIPTA®, NEXTHALER® AND SPIROMAX®.**

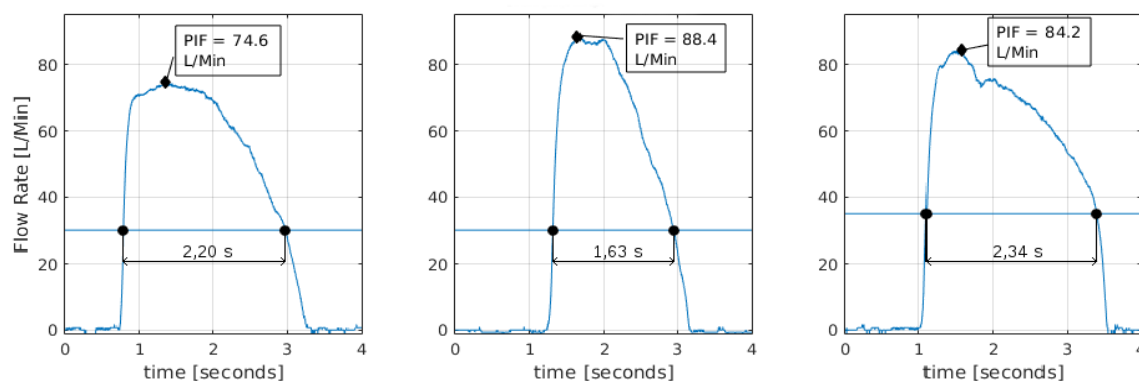
### 3.3 Inhalation maneuver detection

In performing the inhalation maneuvers with the Spiromax® and the Ellipta®, the inhalation rate was uniformly distributed in the range 30-90 L/Min, because 30 L/Min is the minimal inspiratory flow rate that is required for effective treatment (22). In testing the NEXThaler®, the inhalation rate was uniformly distributed in the range 35-90 L/Min, because the breath activated

mechanism (BAM) release the dose only with a flow rate of approximately 35 L/Min (23). All inhalations lasted a minimum of 1 second, as Amiko<sup>®</sup> is intended to record as suboptimal inhalations all maneuvers that occur below this minimum threshold.

### 3.4 Estimating the patient's inspiratory effort

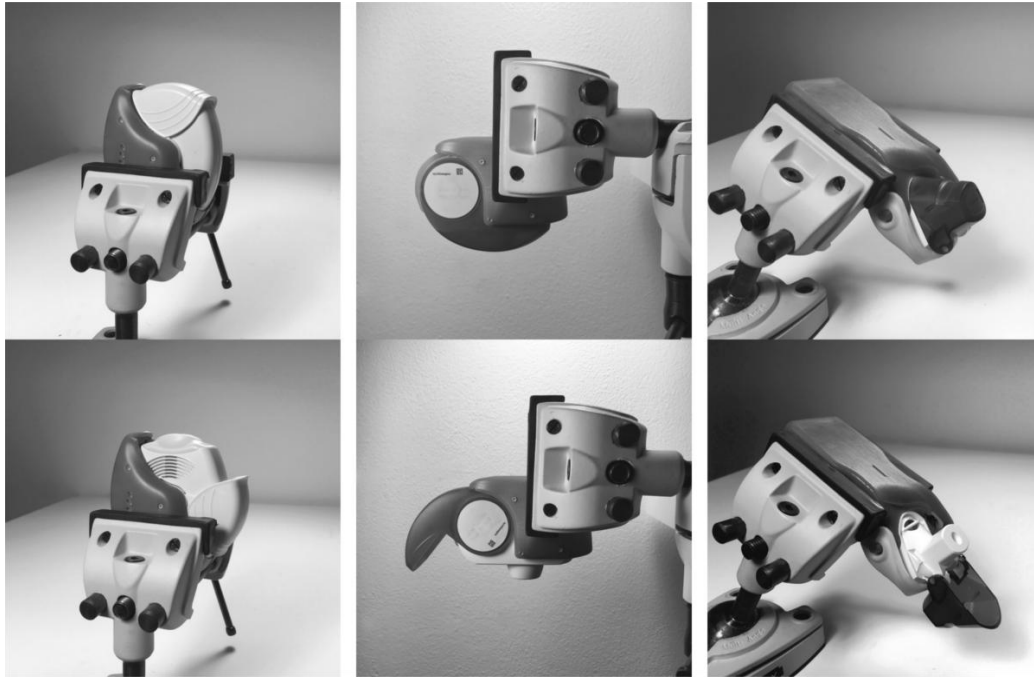
The patient's inspiratory effort was defined by two key parameters of the inhalation profile: the duration of the inhalation and the Peak Inspiratory Flow (PIF). The duration and the PIF were obtained from the inhalations detected in the previously collected dataset. The duration of each inhalation was measured from the flow rate, obtained by converting the signal of pressure into flow. Since the flow was sampled at 500 samples per seconds, the duration of each inhalation was measured by the number of points above the flow thresholds of 30 L/Min for Ellipta<sup>®</sup> and Spiromax<sup>®</sup>, 35 L/Min for NEXThaler<sup>®</sup>, accordingly with the minimum effective flow rate of each inhaler (Fig. 4). Such duration was then compared with the one estimated by Amiko<sup>®</sup> for the inhalations detected. Amiko<sup>®</sup> provides the measure of the duration with a resolution of 64 ms. The PIF was measured on each inhalation as the highest point in the flow rate curve. These measurements were then compared with the values estimated by the Amiko<sup>®</sup> sensors, for the inhalations that were detected.



**FIG. 4 DURATION AND PIF MEASURED ON THREE INHALATION PROFILES ON (LEFT TO RIGHT): ELLIPTA<sup>®</sup>, SPIROMAX<sup>®</sup> AND NEXTHALER<sup>®</sup>. THE DURATION WAS COMPUTED AS THE TIME OF THE FLOW ABOVE THE THRESHOLD OF 30 L/MIN FOR ELLIPTA<sup>®</sup> AND SPIROMAX<sup>®</sup>, 35 L/MIN FOR NEXTHALER<sup>®</sup>.**

### 3.5 Setup C – Loading detection and orientation during inhalation

Another setup was employed to test the accuracy in the detection of loading maneuvers and the accuracy in the estimation of the orientation during inhalations. To perform a correct loading maneuver for Ellipta<sup>®</sup> and Spiromax<sup>®</sup>, the patient needs to fully open the mouthpiece cover until a “click” is heard, which is an audible feedback that signals that the dose is ready to be inhaled (Relvar<sup>®</sup> Ellipta<sup>®</sup> Patient Information Leaflet, GlaxoSmithKline, 2016. DuoResp<sup>®</sup> Spiromax<sup>®</sup> Patient Information Leaflet, Teva Pharmaceuticals, 2015), while for NEXThaler<sup>®</sup> it is sufficient to fully open the cover (Foster<sup>®</sup> NEXThaler<sup>®</sup> Patient Information Leaflet, Chiesi Farmaceutici, 2016). The orientation of the inhaler during the inhalation, defined as the angle between the direction at which the mouthpiece of the inhaler is pointing and the horizontal plane, was also recorded. The inhaler with Amiko<sup>®</sup> was set in a jointed vise at a randomly generated angle between -90° (mouthpiece pointing down) and +90° (mouthpiece pointing up) with steps of 10°, by means of a goniometer (Fig. 5). The inhaler was then loaded by fully opening the cover, for Ellipta<sup>®</sup> and Spiromax<sup>®</sup> until the “click” was heard, then an inhalation was performed with the air vacuum at 60 L/Min for 4 seconds. The cover was then closed back to cover the mouthpiece and the procedure was repeated. The number of loadings recorded by the devices was then compared to the number of loadings performed, and the orientation estimated was then compared with the angle set.



**FIG. 5 (TOP) INHALERS WITH AMIKO® POSITIONED IN A JOINTED VISE WITH DIFFERENT ORIENTATIONS, FROM LEFT TO RIGHT: ELLIPTA®, NEXTHALER® AND SPIROMAX®. (BOTTOM) INHALERS POSITIONED IN THE VISE AFTER THE LOADING MANEUVER IS PERFORMED WITH THE COVER FULLY OPENED.**

#### IV. RESULTS

##### 4.1 Impact on inspiratory flow resistance

The airflow resistance of the two configurations, with and without Amiko, were compared (Tab. 1).

**TAB. 1  
MEASURED RESISTANCES WITH AND WITHOUT AMIKO® FOR THE 3 DPIs AND THEIR DIFFERENCE.**

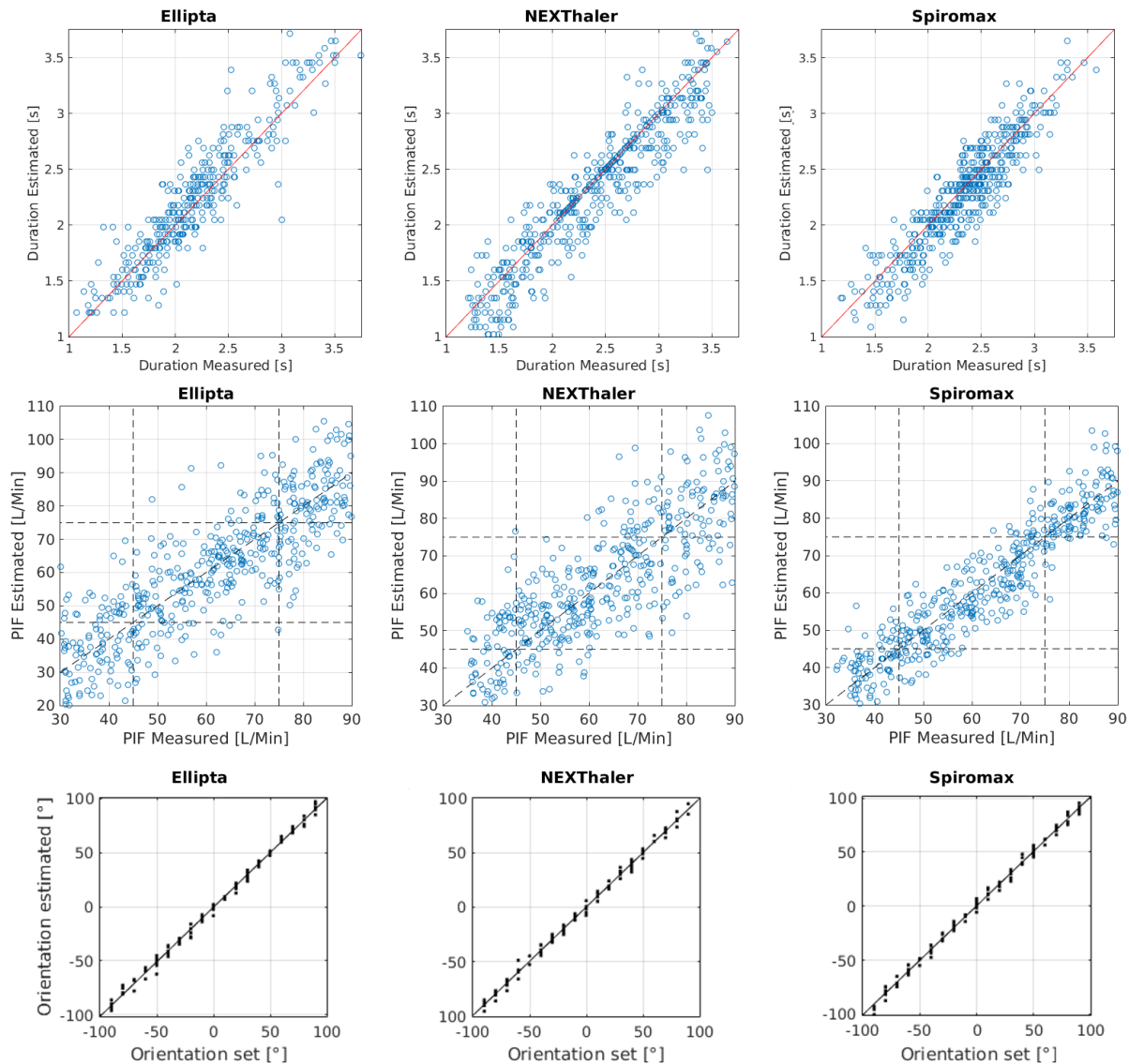
| DPI        | Inhaler's Resistance without Amiko®<br>[kPa <sup>0.5</sup> /(L/Min)] | Inhaler Resistance with Amiko®<br>[kPa <sup>0.5</sup> /(L/Min)] | Difference in Resistance<br>[kPa <sup>0.5</sup> /(L/Min)] |
|------------|--|---|---|
| Ellipta®   | 2.8521 10 <sup>-2</sup>  | 2.8524 10 <sup>-2</sup>   | 3 10 <sup>-6</sup>  |
| NEXThaler® | 3.6132 10 <sup>-2</sup>  | 3.6134 10 <sup>-2</sup>   | 2 10 <sup>-6</sup>  |
| Spiromax®  | 3.1324 10 <sup>-2</sup>  | 3.1326 10 <sup>-2</sup>   | 2 10 <sup>-6</sup>  |

##### 4.2 Inhalation maneuver detection

The inhalation detection was evaluated on 480 maneuvers for each of the three inhalers. For Ellipta® 478 out of 480 (99.58%) inhalation maneuvers were correctly recorded. The inhalations that were not recorded had a PIF of 32.1 L/Min and of 31.8 L/Min. For NEXThaler® and Spiromax®, 479 out of 480 (99.79 %) inhalation maneuvers were correctly recorded. The inhalations that were not recorded had respectively a PIF of 37.3 L/Min and 41.2 L/Min.

##### 4.3 Inhalation duration, PIF and orientation

The values of duration, PIF and orientation, estimated by Amiko® versus the values actually measured, are plotted in Fig. 6. The mean (std) absolute error between the actual duration and the estimate provided by the Amiko® sensors was 0.18 s (0.15 s) for Ellipta®, 0.12 s (0.25 s) for NEXThaler®, and 0.12 s (0.13 s) for Spiromax®. The mean (std) absolute error between the measured and the estimated PIF was 8.16 L/Min (6.52 L/Min) for Ellipta®, 7.95 L/Min (5.81 L/Min) for NEXThaler®, and 4.9 L/Min (3.98 L/Min) for Spiromax®. The mean (std) absolute error for between the set orientation and the orientation estimated was 3.01° (2.48°) for Ellipta®, 3.53° (2.99°) for NEXThaler® and 3.29° (2.54°) for Spiromax.



**FIG. 6: MEASURED VS. AMIKO® ESTIMATED INHALATION DURATION, PIF AND DEVICE ORIENTATION FOR ELLIPTA®, NEXTHALER® AND SPIROMAX®**

#### 4.4 Loading detection

All the loading maneuvers were recorded correctly (240/240) for each DPI, resulting in an accuracy of 100.0%. Loading detection was found to be independent from the orientation of the device and from the inhaler's life cycle, as all loadings were correctly recorded independently from the angle set or the number of doses left in the inhaler.

## V. DISCUSSION

The World Health Organization (WHO) stated that increasing adherence to long-term therapies may have a far greater clinical and economic impact than any improvement in specific medical treatments (26). Poor adherence results in uncontrolled or partly controlled asthma and leads to more frequent symptoms and exacerbations in COPD patients (2,3). Several studies have explored the main factors affecting non-adherence in Asthma and COPD, and the failure of patients to adhere to prescribed treatments or to demonstrate competence with the steps in the administration of inhaled medications, are well known (11). The world of inhalation drug delivery devices has been characterized by a surprising technological evolution in the last decade, resulting from the effort to improve adherence and the quality of inhaled therapies: inhalers are now easier to use, provide patients with instant feedback to promote proper use and ensure a better distribution of the drug within the lung. And now, the wave of mobile health is emerging and is bound to transform the world of inhalation drug delivery devices, inhaled drugs and ultimately, respiratory care. The WHO has recognized the extraordinary relevance of mobile health as a field with the potential to radically transform the overall care process (27) and provide a solution to

improve health and well-being while increasing the systems' quality and efficiency. When it comes to improving respiratory health management and medication adherence, connected inhalers are emerging as one of the most promising mobile health solutions. Electronic monitors for inhalers have been developed since the '80s, in an attempt to provide a more reliable alternative to subjective monitoring of a patient's medication use. Ideally, they should be able to monitor if, when and how a patient is using their inhaler without affecting the functionality of the inhaler itself, and provide access to data useful in assessing adherence and therapeutic response. The current paper provides the experimental performance evaluation of Amiko<sup>®</sup> as an electronic monitoring device, using a range of currently available dry powder inhalers (Ellipta<sup>®</sup>, Spiromax<sup>®</sup> and Nexthaler<sup>®</sup>). Amiko combines sensor technology with proprietary machine learning algorithms to record events or features of the dispenser or the dispensing, including inhaler dose loading, inhalation maneuver, estimation of the patient's inspiratory effort and evaluation of the inhaler orientation during the inhalation. Amiko does not affect the inspiratory flow resistance. In fact, the flow resistance introduced by the monitor (Resistance with Amiko<sup>®</sup> – Resistance without Amiko<sup>®</sup>) was found to be smaller of four orders of magnitude compared to the intrinsic resistance of the inhalers. So the difference in resistance with Amiko<sup>®</sup> can be considered clinically negligible. Amiko<sup>®</sup> was found to be over 99% accurate in detecting the performed inhalation. Furthermore, it provided an estimate of the patient's inspiratory effort, recording the inhalation duration with a mean absolute error smaller than 180ms (0,18 s) and the PIF with a mean absolute error smaller than 8.16 L/Min. All the loading manoeuvres were recorded correctly for each DPI, independently of the orientation of the device, resulting in an accuracy of 100%. Similarly, the tool was able to detect the device orientation during the performed inhalation with a mean absolute error inferior than 3.53° for the three DPIs. All the above reported results suggest that Amiko<sup>®</sup> technology will allow to identify, store and communicate relevant data for adherence improvement and misuse correction. Usability test, efficacy and effectiveness in improving respiratory disease management, need to be explored in clinical research setting and in real life.

#### CONFLICT OF INTEREST

Paa and Ponti works at R&D Department – Amiko Srl. Milan, Italy. Braido and Canonica have any conflict of interest for this paper.

#### REFERENCES

- [1] Guarascio AJ, Ray SM, Finch CK, Self TH The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res.* 2013 Jun 17;5:235-45.
- [2] Gold LS, Montealegre F, Allen-Ramey FC, Jardim J, Smith N, Sansores R, Sullivan SD. Level of asthma control and healthcare utilization in Latin America. *Allergy.* 2013 Nov;68(11):1463-6.
- [3] Demoly P, Gueron B, Annunziata K, Adamek L, Walters RD Update on asthma control in five European countries: results of a 2008 survey. *Eur Respir Rev.* 2010 Jun;19(116):150-7.
- [4] Battaglia S, Basile M, Spatafora M, Scichilone N. Are asthmatics enrolled in randomized trials representative of real-life outpatients? *Respiration.* 2015;89(5):383-9.
- [5] Scichilone N, Basile M, Battaglia S, Bellia V. What proportion of chronic obstructive pulmonary disease outpatients is eligible for inclusion in randomized clinical trials? *Respiration.* 2014;87(1):11-7.
- [6] Belhassen M, Langlois C, Laforest L, Dima AL, Ginoux M, Sadatsafavi M, Van Ganse E. Level of Asthma Controller Therapy Before Admission to the Hospital. *J Allergy Clin Immunol Pract.* 2016 Jul 21. S2213-2198(16).
- [7] Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol.* 1996 Dec;98(6 Pt 1):1051-
- [8] Restrepo RD, Alvarez MT, Wittnebel LD, Sorenson H, Wettstein R, Vines DL, Sikkema-Ortiz J, Gardner DD, Wilkins RL. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis.* 2008;3(3):371-84).
- [9] Sanduzzi A, Balbo P, Candoli P, Catapano GA, Contini P, Mattei A, Puglisi G7, Santoiemma L, Stanziola AA. COPD: adherence to therapy. *Multidiscip Respir Med.* 2014 Nov 22;9(1):60.
- [10] Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique *Chest.* 2000 Feb;117(2):542-50.
- [11] Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, Dekhuijzen R, Sanchis J, Viejo JL, Barnes P, Corrigan C, Levy M, Crompton GK). Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med.* 2008 Apr;102(4):593-604.
- [12] Bender B, Wamboldt F, O'Connor SL, Rand C, Szeffler S, Milgrom H, and Wamboldt MZ. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma & Immunology,* 85(5):416– 421, 2000.
- [13] O'Connor SL, Bender BG, Gavin-Devitt LA, Wamboldt MZ, Milgrom H, Szeffler S, Rand C, Wamboldt FS. Measuring adherence with the Doser CT in children with asthma. *J Asthma.* 2004 Sep;41(6):663-70.

- [14] Gradinarsky L, Loof T. Inhalation adherence monitoring using smart electronic add-on device: Accuracy evaluation using simulated real-life test program. In *Wireless Mobile Communication and Healthcare (Mobi-health)*, 2014 EAI 4th International Conference, pages 145–147, Nov 2014.
- [15] Holmes MS, Seheult J, Geraghty C, D'Arcy S, Costello RW, Reilly RB. Using acoustics to estimate inspiratory flow rate and drug removed from a dry powder inhaler. *Conf Proc IEEE Eng Med Biol Soc.* 2013;2013:6866-9.
- [16] Chan AH, Stewart AW, Harrison J, Camargo CA Jr, Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med.* 2015 Mar;3(3):210-9.
- [17] D'Amato M, Baiardini I, Solidoro P, Braido F Adherence to treatment and monitoring tools: what's new? *Minerva Med.* 2016 Feb;107(1 Suppl 1):5-8. Himes BE, Weitzman ER. Innovations in health information technologies for chronic pulmonary diseases. *Respir Res.* 2016 Apr 5;17:38.
- [18] Minard JP, Turcotte SE, Loughheed MD Asthma electronic medical records in primary care: an integrative review. *J Asthma.* 2010 Oct;47(8):895-912.
- [19] Cegla UH. Pressure and inspiratory flow characteristics of dry powder inhalers: *Respir Med.* 2004 Apr;98 Suppl A:S22-8.
- [20] Grant AC, Walker R, Hamilton M, Garrill K. The ELLIPTA® Dry Powder Inhaler: Design, Functionality, In Vitro Dosing Performance and Critical Task Compliance by Patients and Caregivers. *J Aerosol Med Pulm Drug Deliv.* 2015 Dec;28(6):474-85.
- [21] Prime D, de Backer W, Hamilton M, Cahn A, Preece A, Kelleher D, Baines A, Moore A, Brealey N, Moynihan J. Effect of Disease Severity in Asthma and Chronic Obstructive Pulmonary Disease on Inhaler-Specific Inhalation Profiles Through the ELLIPTA® Dry Powder Inhaler. *J Aerosol Med Pulm Drug Deliv.* 2015 Dec;28(6):486-97.
- [22] Canonica GW, Arp J, Keegstra JR, Chrystyn H. Spiromax, a New Dry Powder Inhaler: Dose Consistency under Simulated Real-World *J Aerosol Med Pulm Drug Deliv.* 2015 Oct;28(5):309-19.
- [23] Corradi M, Chrystyn H, Cosio BG, Pirozynski M, Loukides S, Louis R, Spinola M, Usmani OS. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma. *Expert Opin Drug Deliv.* 2014 Sep;11(9):1497-506.
- [24] Hamilton M, Leggett R, Pang C, Charles S, Gillett B, Prime D. In Vitro Dosing Performance of the ELLIPTA® Dry Powder Inhaler Using Asthma and COPD Patient Inhalation Profiles Replicated with the Electronic Lung (eLung™) *J Aerosol Med Pulm Drug Deliv.* 2015 Dec;28(6):498-506.
- [25] Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers--implications for in vitro testing. *J Aerosol Med.* 1993 Summer;6(2):99-110
- [26] Sabate E, editor. *Adherence to long-term therapies: evidence for action.* Geneva: WHO; 2003.
- [27] WHO Global Observatory for eHealth (2011) *New horizons for health through mobile technologies.* Geneva: World Health Organization. [http://www.who.int/goe/publications/ehealth\\_series\\_vol3/en](http://www.who.int/goe/publications/ehealth_series_vol3/en).
- [28] Khassawneh BY, Al-Ali MK, Alzoubi KH, Batarseh MZ, Al-Safi SA, Sharara AM, Alnasr HM Handling of inhaler devices in actual pulmonary practice: metered-dose inhaler versus dry powder inhalers. *Respir Care.* 2008 Mar;53(3):324-8.
- [29] Bogen D, and Apter AJ: Adherence logger for a dry powder inhaler: A new device for medical adherence research. *J Allergy Clin Immunol.* 2004;114:863–868;
- [30] Smartinhaler by Adherium. Available at <http://www.smartinhaler.com/>.
- [31] Pritchard JN, Nicholls C. *J Aerosol Med Pulm Drug Deliv.* 2015 Apr;28(2):69-81. doi: 10.1089/jamp.2014.1163