

A generic fluticasone propionate and salmeterol dry powder inhaler: Evidence of usability, function, and robustness

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ABSTRACT

Background: A generic combination of fluticasone propionate and salmeterol xinafoate inhalation powder in a premetered, multidose, nonreusable inhaler was recently approved.

Objective: To assess the performance of the generic device.

Methods: Findings from three studies with regard to device usability, function, and robustness were reviewed.

Results: In a study to assess device function in patients and healthy volunteers, the generic device was successfully used by patients with asthma and chronic obstructive pulmonary disease who were either dry powder inhaler users or dry powder inhaler-naïve, even though they were not trained beyond being provided the instructions for use. In a study to measure inhaled flow rates generated by patients and healthy volunteers, the generic device consistently simulated the delivery of a full dose of drug, even to patients with severe respiratory disease and reduced inspiratory flow rates. Although the generic device had a slightly higher airflow resistance, this study demonstrated that this difference did not result in any clinically meaningful differences in terms of drug delivery. Pressure drop, a key parameter that drives the fluidization and aerosolization of the powder dose, was found to be comparable between the devices. In an open-label study, the generic device met all U.S. Food and Drug Administration specifications for device robustness after 21.5 days of twice-daily dosing via oral inhalation among 111 participants with asthma or chronic obstructive pulmonary disease. All inhalers tested demonstrated conformity with a pharmacopeia with respect to key quality parameters (assay, delivered dose uniformity, aerodynamic size distribution). There was no evidence of chemical degradation of the active ingredients, nor of microbial or water ingress into the powder, as a result of inhaler use.

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Dry powder inhalers (DPI) are a broadly accepted form of inhaled drug delivery.¹ As a result of improved usability of DPI devices, they now play an increasingly important role in the treatment of respiratory diseases.² These devices offer patient convenience, for combination therapy in particular, while also improving adherence.¹ The Advair Diskus (GlaxoSmithKline; Research Triangle Park, NC, USA) inhaler is a DPI that contains a combination corticosteroid (fluticasone propionate [FP], 100, 250, or 500 µg) and a long-acting β_2 -adrenergic agonist (salmeterol xinafoate [50 µg]) as an oral inhalation powder.³ Generic products have the potential

to generate significant cost savings for both the health care industry and consumers.⁴

Mylan developed the Wixela Inhub (MGR001 250/50 [containing 250 µg FP and 50 µg salmeterol (as xinafoate salt) inhalation powder, predispensed for oral inhalation in the CRC749 inhaler; (Mylan Pharmaceuticals Inc.; Morgantown, WV, USA) inhaler, a combination of FP and salmeterol inhalation powder predispensed in a novel multidose inhaler that was recently approved as a generic version of the Advair Diskus inhaler.^{5,6} An image of the Inhub inhaler is shown in Fig. 1. The Inhub inhaler has the same indications as the Diskus inhaler: maintenance treatment of asthma in patients ages ≥ 4 years, and for airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD) (250 µg FP/50 µg salmeterol twice daily). The Diskus inhaler contains 60 individually sealed doses of a lactose–drug blend on a blister strip.² Patients operate the inhaler by rotating the mouthpiece cover and sliding a lever that advances the next blister to the dosing position and peels the two sides of the foil blister, which makes the powder available for inhalation.

Wixela Inhub Device Overview

The Inhub inhaler is a nonreusable, premetered, multidose DPI that contains FP (100, 250, or 500 µg)

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Figure 1. Wixela Inhub Inhaler. External and open views. Inhub includes a mouthpiece cover, a lever, and a dose counter.

and a fixed dose of salmeterol (50 µg).⁵ The Inhub inhaler is similar to the Diskus inhaler in size and shape, with the same basic operating steps: open, push or slide, inhale, close.^{3,5} In addition, the Inhub inhaler was designed based on comprehensive human factors studies in which patient feedback was incorporated into an iterative process. Therefore, the Inhub inhaler offers several other features. To make a dose available for delivery to the airway, a lever is pushed down on the Inhub inhaler, whereas the Diskus inhaler requires the user to slide a lever around the perimeter of the device.^{3,5}

Also, minor differences exist between the two devices with regard to airflow resistance. Both are considered medium-resistance inhalers; however, the airflow resistance of the Inhub inhaler is slightly higher than the airflow resistance of the Diskus inhaler.⁶ A study that compared the two devices showed a mean airflow resistance of 0.034 kPa_{1/2}/L/min⁻¹ for the Inhub inhaler and 0.027 kPa_{1/2}/L/min⁻¹ for the Diskus inhaler.⁷ In addition, device resistance was found to be more reproducible with the Inhub inhaler when compared with the Diskus inhaler. The Inhub inhaler has also demonstrated less variability of emitted dose delivery at a flow rate of 30 L/min and thus maintains better *in vitro* performance than the Diskus inhaler at low flow rates.⁷

However, this observation is unlikely to have any clinical significance because all the patient groups in this study achieved flow rates well over 30 L/min from the Diskus inhaler. The Inhub inhaler was also designed so that an open dose pocket is only available for inhalation until the device is closed again, so that patients cannot receive a double dose. If a patient actuates the device but does not inhale and closes the device, then the dose from the Diskus inhaler is still available to inhale the next time the device is used. Also, the Inhub inhaler was designed with a larger dose counter (double the size of that of the Diskus

inhaler) to improve readability and will lock out when the dose counter reaches 0 and no doses remain.⁵

Review of Inhub Inhaler Studies

In this article, we reviewed the findings from three Inhub inhaler studies with regard to device usability, function, and robustness.

Study 1: Human Factors Usability Validation Study. A human factors usability validation study was conducted with patients with asthma, COPD, or both, to demonstrate that the Inhub inhaler can be used by representative end users to deliver a therapeutic dose safely and effectively according to predefined success criteria.⁸ This study was also intended to demonstrate the low likelihood of device use error that would result in a patient receiving a subtherapeutic dose among the Diskus inhaler users and those with no previous DPI experience, with a specific focus on orientation of use.⁸ The study enrolled a total of 110 participants (55 Advair Diskus inhaler users [ADUs] and 55 DPI-naïve users).⁸ The participants were further segmented into age groups (≥12 to <18 years, ≥18 to <65 years, and ≥65 years).⁸

Without training, verbal instruction, or prompting, the participants in this human factors study were provided with the inhaler in packaging representative of the commercial packaging and were encouraged to use the inhaler as they would in a home environment.⁸ The participants were only provided with the written instructions for use (IFU) and were asked to use the inhaler three times to capture their actual “at-home” use. All the participants demonstrated taking three doses with an empty Inhub inhaler. The participants were evaluated based on a prespecified set of criteria.⁸ The success criteria and the results for the third simulated Inhub dose are shown in Table 1.

The most common observation made, based on the success criteria, was of participants not holding the Inhub in the vertical position; 8 of the 10 participants who held the Inhub inhaler in the horizontal position were in the ADU group.⁸ The participants in the ADU group who did not read the IFU in any of the first three simulated doses were five times more likely to hold the Inhub in the horizontal orientation during the third simulated inhalation.⁸

The participants who held the Inhub in the horizontal position were asked to perform three additional inhalations by using an instrumented device to determine whether they would achieve inhaled flow rates and inhaled volumes necessary for satisfactory drug delivery. Nine of the 10 participants (90%) who held the Inhub inhaler in the horizontal position achieved an inhaled flow rate of >30 L/min and an inhaled total

volume of >1 L/min.⁸ For the single participant who did not meet the flow rate and total inhaled volume targets, it was determined that orientation alone was not the cause because this participant was not able to achieve the target flow rate and total inhaled volume with the device held in either orientation.

Study Conclusions. The participants in this study were able to successfully simulate the delivery of a therapeutic dose by using the Inhub inhaler when provided only with the IFU, with no safety issues, even in a worst-case scenario in which patients would not receive any training on Inhub use. The most common observation was of using the Inhub in a horizontal rather than in a vertical position; however, based on observed flow rates and total inhaled volume when used in the horizontal position, patients would still receive a therapeutic dose.

Study 2: Inhaled Flow Rates in Patients and Healthy Volunteers. An open-label, 2 × 2 crossover study was conducted to measure inhaled flow rates for the Diskus and Inhub inhalers generated by patients and healthy volunteers.⁷ The primary objective of this study was to determine inhalation profile parameters from empty Inhub and empty Diskus inhalers when used by participants with severe COPD or asthma, pediatric participants with asthma, and healthy volunteers. The primary end point of the study was peak inspiratory flow rate (PIFR). Safety was assessed based on physical examinations and documentation of adverse events (AE). The participants were provided with training on how to inhale rapidly and deeply through both the Inhub and Diskus inhalers. Once they were trained, they were instructed to inhale rapidly and deeply through both devices to generate three inhalation profiles for each device, with the device sequence being randomized.

Table 1 Success criteria and results, final simulated Inhub inhaler dose

Criteria	Completed Successfully, n (%) (N = 110)
User is able to open the mouthpiece cover	110 (100)
User pushes the lever as far as it will go	108 (98)
User leaves the lever fully pushed during inhalation	108 (98)
User holds the inhaler in the vertical orientation	100 (91)
User fully closes the mouthpiece cover for storage	110 (100)

The PIFRs and pressure drop were measured by using instrumented Inhub and Diskus inhalers. The inhalation profile (inspiratory flow rate and pressure drop as a function of time) were determined by using a validated, computer-driven inhalation profile system. The pressure drop was recorded by a pressure transducer that measured the pressure drop created at the mouthpiece of the device when a participant inhaled through it. Software converted the pressure data to provide PIFR and the peak pressure drop across the internal resistance of the device. A total of 80 participants were randomized into one of five groups (healthy adults [ages, 18–60 years], children with asthma [ages, 4–7 years], children with asthma [ages, 8–11 years], adults with asthma, and adults with severe COPD).⁷ The PIFRs and peak pressure drop values are shown in Table 2.

The flow rates reported in this study were consistent with expectations based on the resistance of the two devices. Across all groups, slightly lower PIFRs were observed for the Inhub inhaler compared with the Diskus inhaler.⁷ Despite minor differences in resistance, all the participants in this study exhibited PIFRs of >30 L/min.⁷ Except for the participants with severe COPD, the mean peak pressure drop values were slightly higher in the Inhub inhaler groups compared with the Diskus inhaler groups.⁷

Study Conclusions. Healthy adult participants, adult participants with severe COPD or asthma, and children with asthma generated lower PIFRs when using the Inhub inhaler than when using the Diskus inhaler.⁷ These results were consistent with expectations because the Inhub inhaler has a higher airflow resistance than the Diskus inhaler; however, the differences in PIFRs were not considered clinically significant because, in this study, the difference in airflow resistance between Inhub and Diskus inhalers did not result in any clinically meaningful differences in terms of the PIFR that determines adequate drug delivery.⁷ This determination was supported by the comparability in pressure drop, a key parameter driving the fluidization and aerosolization of the powder dose, for the Inhub inhaler and the Diskus inhaler groups.

Study 3: Robustness of the Inhub Inhaler. An open-label study was conducted to assess the in-use robustness of the Inhub inhaler device and pharmaceutical performance after twice-daily dosing of Inhub inhaler administered *via* oral inhalation in the participants with asthma or chronic COPD.⁸ The primary objective was to confirm the robustness of the Inhub inhaler after 21.5 ± 3 days of twice-daily dosing of the Wixela Inhub inhaler containing 250 µg FP and 50 µg salmeterol inhalation powder.⁸ A study period of <30 days was selected to allow the return of unused product for testing. The product was considered robust if the

Table 2 Inhaler device function study: peak inspiratory flow rates and peak pressure drop

	Healthy Adults (<i>n</i> = 10)		Children with Asthma (4–7 years) (<i>n</i> = 20)		Children with Asthma (8–11 years) (<i>n</i> = 20)		Adults with Asthma (<i>n</i> = 14)		Adults with Severe COPD (<i>n</i> = 14)	
	Diskus	Inhub	Diskus	Inhub	Diskus	Inhub	Diskus	Inhub	Diskus	Inhub
Peak inspiratory flow										
<i>n</i>	10	10	20	20	20	20	14	14	14	14
Peak inspiratory flow rates, mean ± SD, L/min	120.7 ± 9.48	86.3 ± 7.58	66.8 ± 16.32	50.6 ± 11.13	100.6 ± 10.07	75.4 ± 9.53	102.9 ± 12.75	74.8 ± 8.99	94.9 ± 8.96	69.5 ± 6.36
Highest value achieved in three inhalations										
Peak inspiratory flow rates, mean ± SD, L/min	124.1 ± 9.11	88.6 ± 7.24	72.0 ± 16.48	53.2 ± 10.85	105.2 ± 9.59	79.1 ± 7.79	106.5 ± 13.03	76.5 ± 9.06	98.2 ± 8.63	70.8 ± 6.65
Peak pressure drop										
<i>n</i>	10	10	20	20	19	19	14	14	14	14
Peak pressure drop, mean ± SD, kPa	8.58 ± 1.33	9.14 ± 1.58	2.78 ± 1.23	3.27 ± 1.40	5.99 ± 1.13	7.05 ± 1.62	6.30 ± 1.67	6.90 ± 1.75	5.39 ± 0.99	5.93 ± 1.13

COPD = Chronic obstructive pulmonary disease; SD = standard deviation.

returned Inhub inhalers (in testable condition) met the proposed commercial specifications on *in vitro* testing of the pharmaceutical performance of FP and salmeterol remaining in the Inhub inhaler.

A total of 111 participants, ages ≥12 years, with asthma or COPD received 3 weeks of the Wixela Inhub 250/50 (FP 250 µg and salmeterol [as xinafoate] 50 µg inhalation powder predispensed in the Inhub inhaler) inhaler twice daily.⁸ The participants were trained on the use of the Inhub inhaler and, subsequently, were retrained as necessary if the investigators noted any noncompliance with the IFU. The first dose was taken in the clinic, after which the Inhub inhaler was dispensed to the participant for outpatient use in a real-life dosing environment. The participants were also provided a diary to record dosing and AEs. After 3 weeks of dosing, the participants returned to the clinic, where they received their final dose.⁸

The inhalers were then returned to the investigator and subsequently sent for testing within 7 days of the participants' last dose. The inhalers were submitted for *in vitro* testing of pharmaceutical performance of the unused drug if participants used ≥16 days of twice-daily dosing, confirmed *via* the dose counters and participant diaries.⁸ Compliance was confirmed if the dose counter read ≤28, which equates to compliance with ≥75% of protocol dosing (*i.e.*, ≥32 doses were used, which equated to ≥16 days of twice-daily dosing).⁸ At the testing laboratory, an external visual inspection was performed to assess for damage or defect to determine suitability of the inhaler for testing.⁸

The robustness of the Inhub inhaler was assessed by *in vitro* testing of pharmaceutical performance, including microbiology, emitted dose content uniformity, aerodynamic particle size distribution, assay, and degradation products based on the criteria as described by Allen *et al.*⁸ Patient safety assessments included a physical examination, 12-lead electrocardiogram, vital signs, spirometry (forced expiratory volume in 1 second [FEV₁] and forced vital capacity), and spontaneously reported AEs.

All 111 inhalers were returned, of which 107 were deemed available for *in vitro* testing of pharmaceutical performance. Thirteen of the 107 inhalers underwent a temperature excursion during transportation and were deemed suitable only for water-content assessment. A total of 84 inhalers were required for testing; therefore, testing was not performed on the remaining 23 inhalers. All inhalers tested demonstrated conformity with the United States Pharmacopeia monograph specification⁹ with respect to key quality parameters (assay, delivered dose uniformity, aerodynamic size distribution). There was no evidence of chemical degradation of the active ingredients, nor of microbial or water ingress into the powder, as a result of inhaler use. Therefore, the Inhub inhaler was found to be robust.

Table 3 Summary of studies and key findings

Study	Description	Conclusions
Human factors usability study	To demonstrate that the Inhub inhaler can be used by representative end users to deliver a therapeutic dose safely and effectively according to predefined success criteria	The participants in this study were able to successfully simulate the delivery of a therapeutic dose by using the Inhub inhaler when provided only with the IFU, with no safety issues
Inhaled flow rates	Open-label, 2 × 2 crossover study to measure inhaled flow rates for the Diskus inhaler and the Inhub inhaler generated by patients and healthy volunteers	Healthy adult participants, adult participants with severe COPD or asthma, and children with asthma generated lower PIFRs by using the Inhub inhaler than by using the Diskus inhaler; the difference in airflow resistance between Inhub and Diskus inhalers did not result in any clinically meaningful differences in terms of the PIFR that determines adequate drug delivery
Robustness of the Inhub inhaler	An open-label study to assess the in-use robustness of the Inhub device and pharmaceutical performance after 21.5 ± 3 days of twice-daily dosing of the Wixela Inhub 250/50 inhaler in participants with asthma or COPD	Comprehensive <i>in vitro</i> testing confirmed the robustness of the Inhub inhaler; results from <i>in vitro</i> testing and visual inspection after anticipated real-life handling were as expected and all within the Inhub inhaler product specifications; the Wixela Inhub 250/50 inhaler was shown to be safe and well tolerated among the participants with asthma and COPD, including adolescent and elderly participants

IFU = instructions for use; COPD = chronic obstructive pulmonary disease; PIFR = peak inspiratory flow rate.

The safety analysis set consisted of all the participants who received one or more doses of the study drug and included 111 participants.⁸ A total of 108 participants (97.3%) completed the study. Two participants discontinued the study due to protocol deviation (neither could attend study visits), and one participant discontinued the study due to an AE (atrial fibrillation of mild intensity), which was considered unlikely to be related to the study drug by the study investigator.⁸ A total of 55 AEs were reported by 34 participants (30.6%).⁸ The vast majority of AEs were mild in nature: 33 participants (29.7%) reported AEs that were mild, and 1 participant (0.9%) had an AE that was moderate.⁸ No serious AEs were reported in this study; the most frequent AEs were headaches (11 participants [9.9%]), dysphonia (4 participants [3.6%]), and oropharyngeal pain (4 participants [3.6%]).⁸

Study Conclusions. The outcomes of comprehensive *in vitro* testing confirmed the robustness of the Inhub inhaler after >21.5 days of twice-daily dosing *via* oral

inhalation of the Wixela Inhub 250/50 inhaler among devices with ≥75% compliance of per protocol dosing.⁸ The results from *in vitro* testing and visual inspection after anticipated real-life handling were as expected, and were all within the Inhub product specifications. In addition, the Inhub 250/50 inhaler was shown to be safe and well tolerated among participants with asthma and COPD, including adolescent and elderly participants.⁸

DISCUSSION

The Wixela Inhub inhaler was approved by the U.S. Food and Drug Administration and demonstrates bioequivalence to the Advair Diskus inhaler.^{3,5} The Inhub and Diskus inhalers are both premeasured, multidose, nonreusable DPIs. The Inhub inhaler contains the same active ingredients as the Diskus inhaler, is expected to deliver the same efficacy and safety profile, and is approved for the same indications.

In this article, we reviewed three studies with regard to the Inhub inhaler.^{7,8} A summary of these studies, along with key findings, is shown in Table 3. In a study to assess device usability in patients and healthy volunteers, the Inhub inhaler was successfully used by representative end users, including patients with asthma and COPD who were Diskus inhaler users or DPI naive.⁸ The participants in this study were able to successfully simulate the delivery of a therapeutic dose by using the Inhub inhaler, with no safety issues, even though they were not provided any specific training beyond being provided the IFU and being asked to use the inhaler to capture their actual “at-home” use. The Inhub inhaler is intended to be oriented vertically during use, whereas the Diskus inhaler is intended to be used horizontally. Despite this difference, the results from this study indicated a low likelihood of orientation-related errors during Inhub inhaler use. In this study, 91% of the participants inhaled from the Inhub with the device in a vertical position, and 99% of the participants would have been expected to receive a full dose.

In a study to measure inhaled flow rates for the Inhub inhaler generated by patients and healthy volunteers, the Inhub inhaler consistently simulated the delivery of a full dose of drug, even to patients with severe respiratory disease and moderately to severely reduced FEV₁ values.⁷ This study demonstrated that the difference in airflow resistance between the Inhub and Diskus inhalers did not result in any clinically meaningful differences in terms of drug delivery.⁷ In this study, all the participants exhibited PIFRs >30 L/min, and the peak pressure drop, a key parameter that drives the fluidization and aerosolization of the powder dose, was comparable for the Inhub and Diskus devices.⁷

In an open-label study, the in-use robustness and pharmaceutical performance of the Inhub inhaler was assessed after 21.5 days of twice-daily dosing of the Inhub 250/50 inhaler administered *via* oral inhalation in 111 participants with asthma or COPD.⁸ In this study, the results from *in vitro* testing and visual inspection by following anticipated real-life handling among devices with ≥75% of per protocol dosing were as expected and were all within the Inhub product specifications.⁸

Limitations

A limitation of the studies reviewed here was the focus on device usability, inhaled flow rates among patients and healthy volunteers, and device robustness, rather than on clinical outcomes such as asthma control or impact on health-related quality of life. As a result, no conclusions can be drawn with regard to the clinical efficacy of the Wixela Inhub inhaler based on these studies. Another limitation of these studies was their short duration (≤4 weeks); as a result, no long-term data were presented or reviewed.

CONCLUSION

Across all the studies, the Wixela Inhub inhaler demonstrated an excellent safety profile and was well tolerated.

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