FACTORS TO CONSIDER IN DEVELOPING A DRY POWDER INHALER

David L. Gardner, Ph.D.
Respirics, Inc.

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Inhalation Delivery Systems

- Nebulizers (SVN)
  - liquid or suspension
  - jet/ultrasonic
  - small mist nebulizers (Respimat®, AER$_x$®, Mystic®)
- Metered Dose Inhalers (MDIs)
  - solution or suspension (CFC vs. HFA)
  - breath-activated inhalers (Autohaler®, Easi-Breathe®)
- Dry Powder Inhalers (DPIs)
  - capsule
  - single or multi-dose blisters
  - reservoir

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Advantages of Nebulizers

- Normal tidal breathing-little coordination
- High doses of medication
- Can use multiple drugs
- Suitable for specific age groups
- Treatment of CF patients-antibiotic

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Disadvantages of Nebulizers

- Length of time to nebulize
- Equipment can be large (difficult to transport)
- Need for external power source
- Variability in performance between different nebulizers

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MDI Advantages

- Mainstay of pulmonary delivery since 1950’s
- Capacity for large number of doses
- Unit dose cost is low
- Compact and portable

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MDI Disadvantages

- Co-ordination of actuation with inhalation
- Knowing how many doses remain
- Drug content/dose is problematic if MDI not shaken-suspensions
- Contribution to depletion of ozone layer
- Limited to certain drugs that are stable in a propellant
- Potential for oropharyngeal drug deposition
- Mental/cognitive ability of older generation

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Transition of MDIs to DPIs

- DPIs appeared on market in 1971 - Spinhaler®
- Eliminate ozone depletion concern of either CFC or HFA-based propellants
- Increased drug stability – dry powder
- Accurate pre-metering of dose
- Success of Turbuhaler® (Pulmicort®, Symbicort®) and Diskus® (Advair®)

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Examples of U.S. DPIs

- Spinhaler® (capsule) 1971 cromolyn sodium NLA
- Rotahaler® (capsule) 1988 albuterol sulfate NLA
- Diskhaler® (blister cartridge) 4 doses fluticasone propionate NLA
- Diskus® (blister tape) 60 doses salmeterol xinofoate (Serevent®), salmeterol xinofoate + fluticasone propionate (Advair®)

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Examples of U.S. DPIs (Con't)

- Turbuhaler® (reservoir) 200 doses budesonide (Pulmicort®), budesonide + formoterol (Symbicort®)
- Aerolizer® (capsule) formoterol
- Handihaler® (capsule) tiotropium bromide
- Twisthaler® (reservoir) 14, 30, 60 and 120 doses mometasone furoate

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DPI Disadvantages

- Requires moderate inspiratory effort (related to DPI resistance to flow)
- Few drugs available in multi-dose format
- Difficulty in operational steps
- Moisture ingress-aggregation and stability
- Number of doses available-unit cost/dose

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Drug Factors

- Preparation of drug powder
  - Milling, spray drying, supercritical fluids
- Crystalline vs. amorphous
- Polymorphism-effect on solubility and hygroscopicity
- Hygroscopic drugs-more risk of instability
- Hygroscopicity may alter adhesive/cohesive properties

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DPI/Formulation Factors

- Identify interactions of formulation with device
- Drug powder interparticulate forces
- Protection of drug powder from moisture (stability)
- Powder retention
- Resistance to airflow
- Number / volume of doses
- Filling / metering of powder
- Flowability of drug powder

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Drug/Carrier Interaction Factors

- Surface properties of the drug and carrier (roughness)
- Ratio of drug to carrier
- Particle size of each component
- Relative humidity
- Electrostatic behavior
- Processing conditions (batch size)
- Segregation during processing, filling, and storage

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Powder Deaggregation Factors

- Minimize cohesive/adhesive particle forces
- Minimize electrostatic charging of particles
- Neat drug vs. carrier/drug particle size
- Hygroscopic vs. non-hygroscopic particles
- Inspiratory flow rate
- Baffles/deaggregation channels

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DPI Patient Factors

- Technique errors (correct positioning, exhaling into mouthpiece, no breath hold)
- Complication of devices (too many steps…)
- Generating sufficient inspiratory flow
- Demonstration and training of correct use (RTs, nurses, physicians)

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Peak Inspiratory Flow Rate (PIFR)

- Correlation between PIFR and device resistance
- In general, dose delivery increases with air flow
- Variability in dose delivery is tolerable if working with wide therapeutic drugs
- Some resistance may be good since it opens the airways
- Most asthmatics and COPD patients have little difficulty in achieving flow rates of 45L/min

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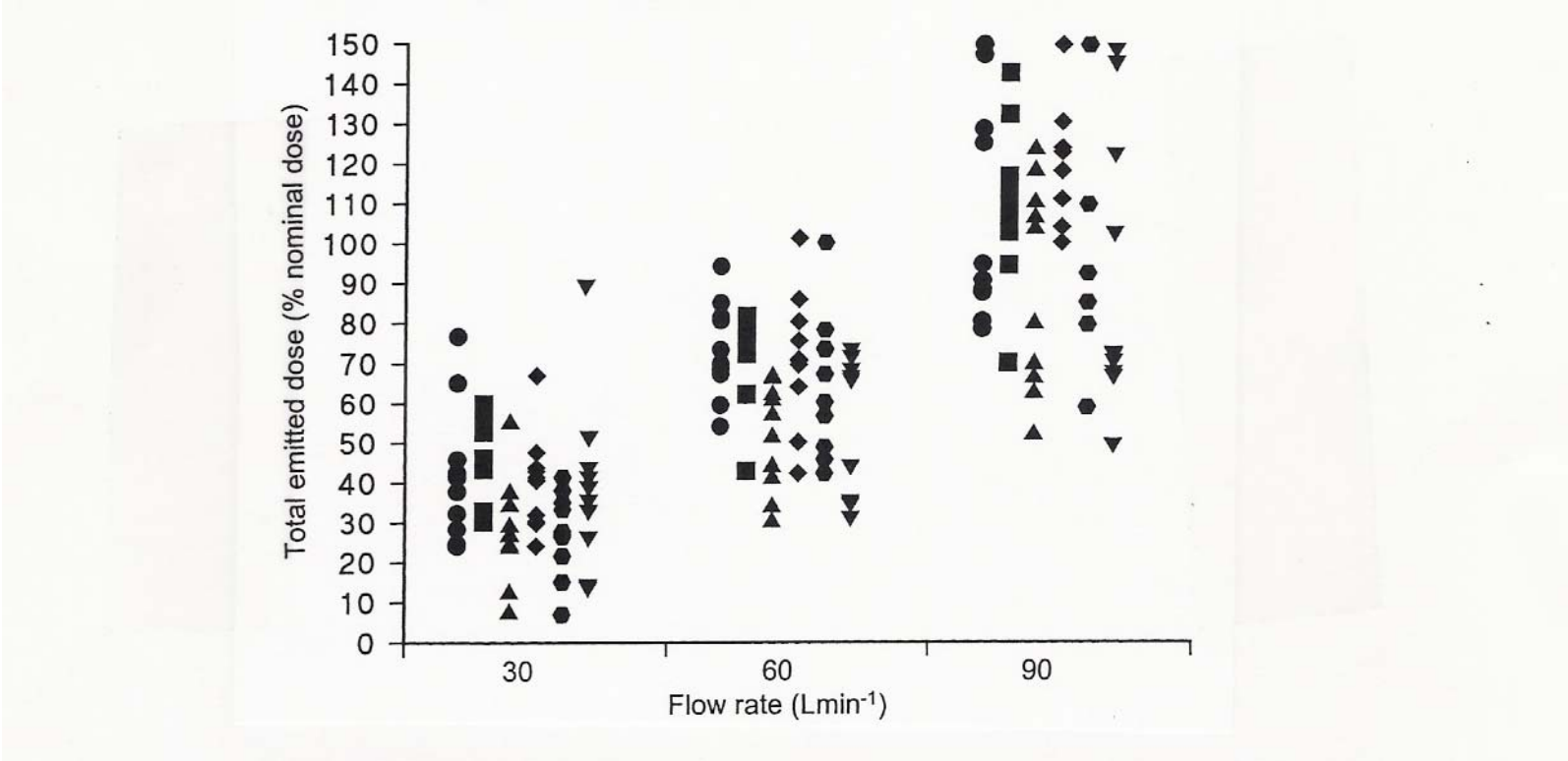
Budesonide % Emitted Dose



Testing of six Symbicort Turbuhalers at three different flow rates (formoterol component showed same trend)

Tarsin et al., J. Aerosol Medicine, Vol. 17(1),pp 25-32, 2004.

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Peak Inspiratory Flows

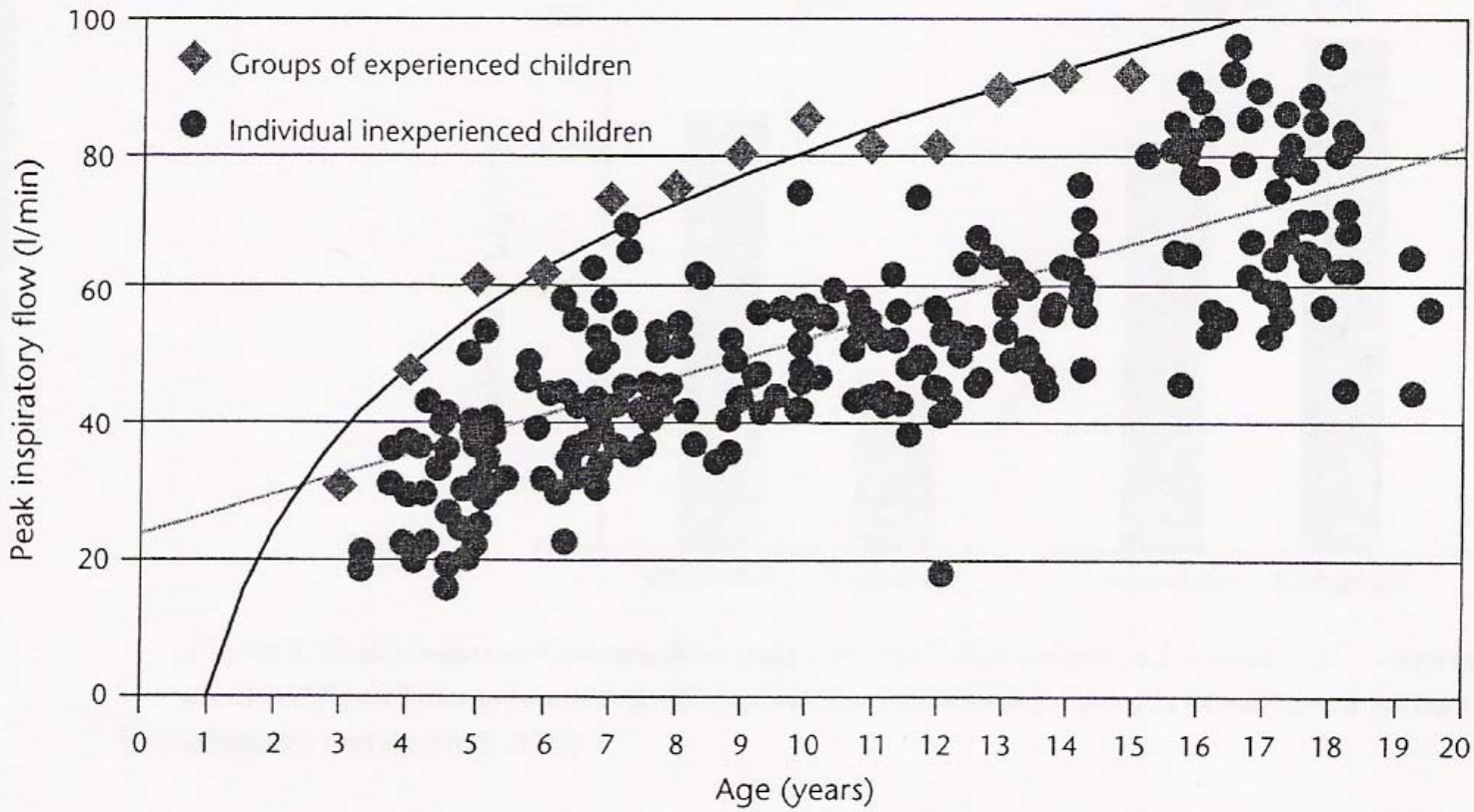

Figure 1. *Peak inspiratory flows in individual inexperienced children (Pedersen* et al, *1990) and groups of experienced children (Agertoft* et al, *1995).*

S. Pedersen, Journal of Aerosol Medicine, Vol.10, Suppl 1, p.41-44, 1997

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One Scenario For DPI Development

- Identify the market you want to pursue
  - Disease state and patient population
- Review the patent literature covering that market
- Create concepts/designs for your DPI
- Perform preliminary FEMA
- Create SLA prototypes (quick turnaround)
- Preliminary evaluation of SLA prototype performance and conduct focus group studies

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One scenario For DPI Development (con't)

- Iterations of formulation with DPI
- Iterations of device design (prototypes)
- Retest of formulation and device
- Prepare single cavity tooling
- Laboratory testing
- Preparation of cGMP formulation
- Stability testing of formulation in device
- Clinical testing
- Prepare multi-cavity tooling

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Acu-Breathe™ Product Line

Single-dose inhaler
Reusable Device

15-dose inhaler
Reusable Device
Replaceable Cartridge
Dual piercer

30-dose inhaler
Disposable Device
Dual piercer

Drug Delivery Technology, Vol 5 No 4, April 2005.

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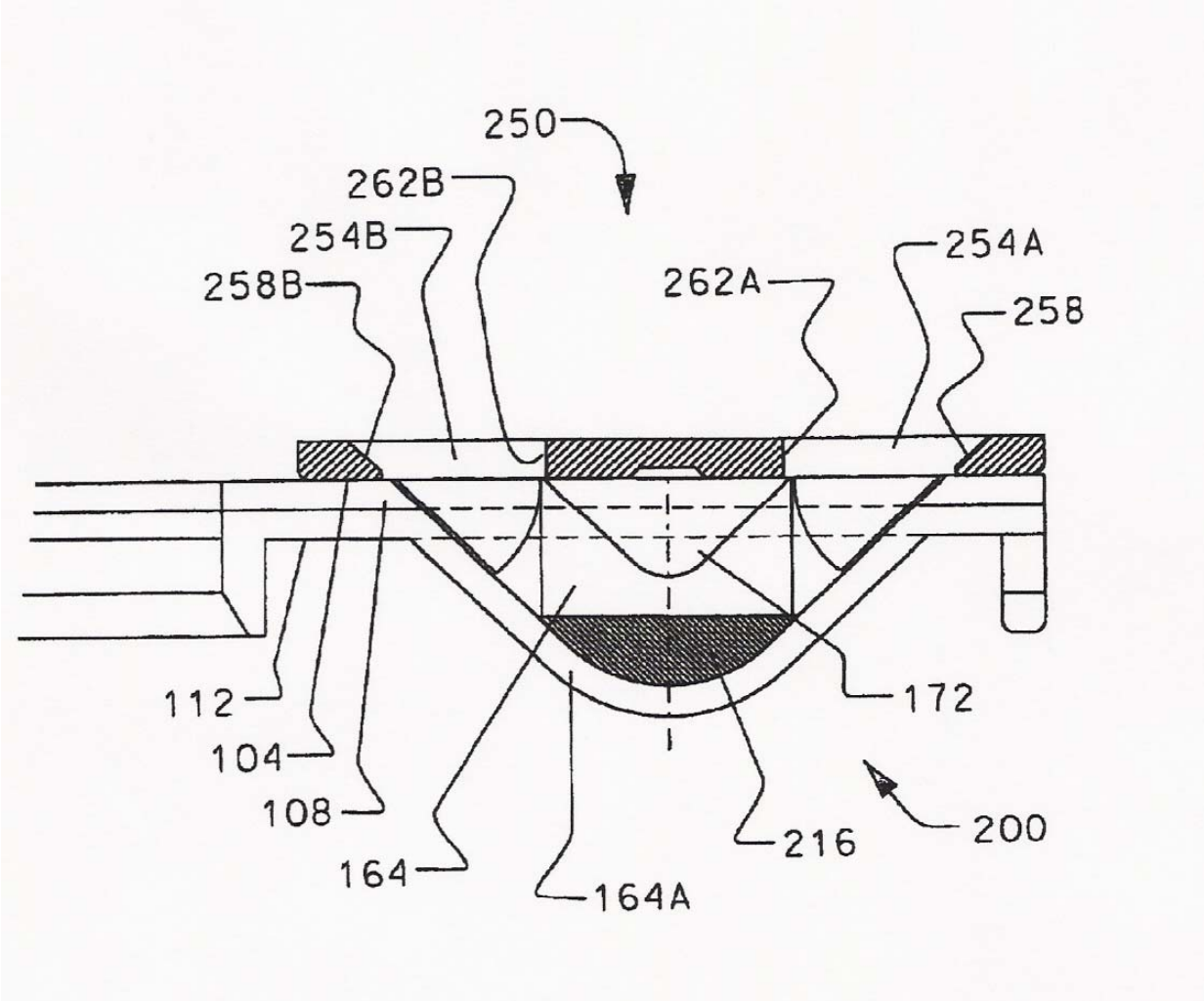
Dual Piercing Mechanism



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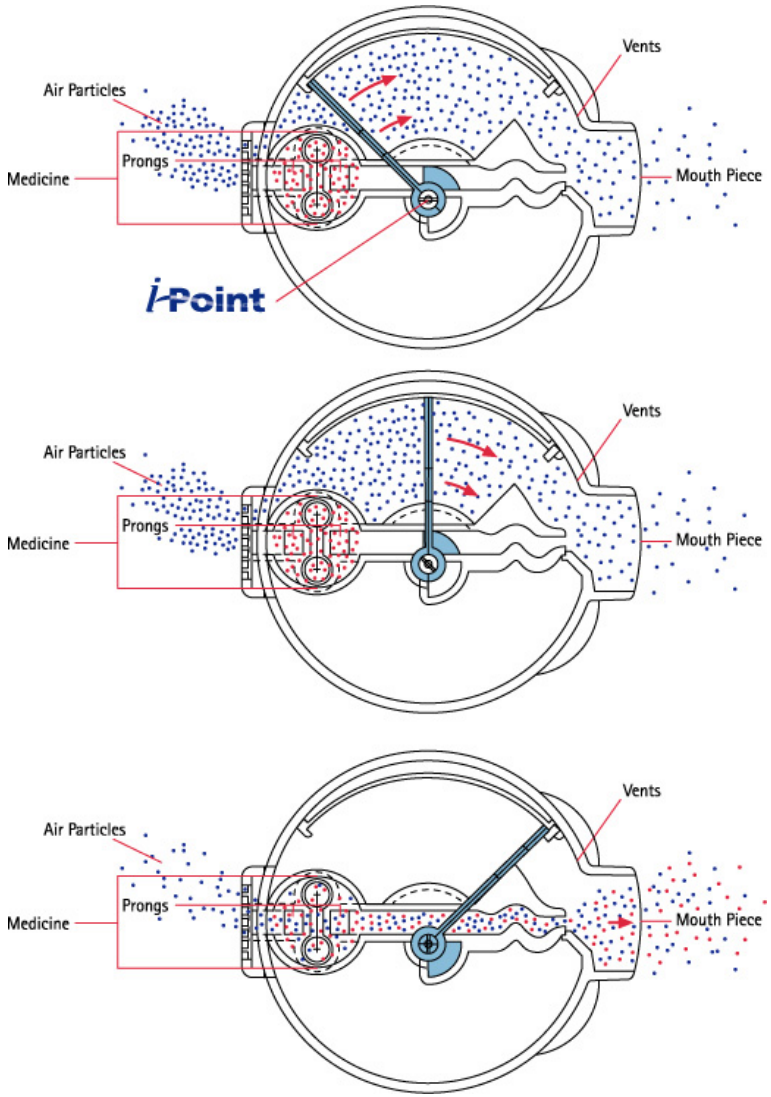
Acu-Breathe: I-Point Mechanism



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Acu-Breathe 30-Dose

- **Device Image**

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Acu-Breathe 30-Dose

- **30-dose cartridge exposed**

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Comparison of Diskhaler and Acu-Breathe – Fluticasone propionate

Device Tested n = 3	Labeled/Blister Dose, µg	Respirable Mass, µg	Blister Residual, µg	Respirable Fraction, %
Diskhaler™ (no FP powder transfer)	250 ± 0.0	36.6 ± 2.2	29.1 ± 6.2	14.6 ± 0.8
Diskhaler™ (FP powder transfer)	248 ± 9.4	33.8 ± 2.6	23.3 ± 2.9	13.7 ± 1.5
Acu-Breathe™ 15-dose (FP powder transfer)	230 ± 8.7	36.2 ± 2.5	6.8 ± 2.1	15.8 ± 1.0

Cascade impactor experiments tested at 60L/min

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Comparison of Diskhaler™ and Acu-Breathe™ – fluticasone propionate

Device Tested	Exp. #	FP Blister Load, µg	Respirable Mass, (Stages 1-filter), µg	Respirable Fraction, %**	(Pre-separator, TPS, Stages 0-filter), µg	Left in Blister & device %	Emitted Dose %**
Acu-Breath™ 30-dose	1	249.5*	42.7	17.1	221.1	11.4	88.6
Acu-Breath™ 30-dose	2	250.1*	41.6	16.6	228.0	8.8	91.2
Acu-Breath™ 30-dose	3	250.3*	38.3	15.3	235.0	6.1	93.9
Diskhaler®	1	250*	43.0	17.2	174.5	30.2	69.8
Diskhaler®	2	250*	39.0	15.6	181.9	27.2	72.8
Diskhaler®	3	250*	43.3	17.3	196.7	21.3	78.6

Cascade impactor experiments tested at 60L/min

* Based upon six weighed amounts of the FP/lactose blend placed in each of six cartridge blisters or label claim of the Flovent® Rotadisk® product

** Based upon blister load

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Acu-Breathe™ Design Attributes

ATTRIBUTE	**BENEFIT**
• Individual drug blisters	Improved shelf-life
• *i-Point*™ breath triggered	Dose-to-dose consistency
• Low part count & simple design	Ease of manufacture (cost)
• Broad drug payload capacity	Formulation and future product flexibility
• Compact size & simple to use	Patient acceptance
• Dual air path and valve design	Dose protected from accidental exhalation
• Double-dose prevention • Dose counter • Patient friendly (3-step operation)	**Regulatory attractiveness**

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Acu-Breathe™ Design Attributes (Cont.)

ATTRIBUTE	BENEFIT
• Unique blister design • Dual piercing mechanism	Improved blister clearance
• Large blister capacity (25mg)	Broad formulation compatibility
• Air vane audible feedback	Confirmation of delivered dose
• Zigzag delivery channel	Maximal de-agglomeration of powder
• Customizable breath trigger	Can fine-tune device to formulation

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