



Metered Dose Inhalers (MDIs)

In Vitro Measures to Confirm Patient Perceptions: HFA vs. CFC

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The information presented here represents the
opinions of the author and is not intended to convey
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Outline

- General Problems that need to be addressed
- Problems specific to MDIs (and other Orally Inhaled Drugs, OIDs)
- Some solutions
- Areas of current study at DPA



General Problems with Pharmaceuticals

- Patient training by pharmacists and prescribers is inadequate
- Better Labeling is needed ^{1,2,3}
 - **46% of patients misunderstood one or more dosage instructions**
 - **56% misunderstood one or more auxiliary warnings**
 - **Particularly troublesome for low-literacy patients**

¹ *Pharmaceutical Forum*, **37**(1) [Jan.–Feb. 2011]

² *Federal Register*, **76**(46), 12969 (March 9, 2011)

³ Draft Guidance for Industry on Medication Guides, Docket No.FDA-2011-D-0074



General Problems

- These problems observed for solid oral dosage forms
- How much worse for complex OIDs?
- Patient use – What is our role?
 - Insert instructions
 - Training
 - Product design
 - Other



Areas of Concern

- Of \$25 billion spent annually on inhalers, \$5-7 billion is wasted due to patient misuse leading to inadequate dosing³
 - Misuse ranges between 4% - 94%⁴
- Only 2 of 40 medical texts surveyed included a list of steps for MDI use
- Differences between “performance” of HFA-MDIs vs. CFC-MDIs

³ Fink, JB, Rubin, BK 2005. Problems With Inhaler Use: A Call for Improved Clinician and Patient Education. *Respiratory Care* 50(10):1360-1375.

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Specific Problems

- Actuation/inhalation synchronization
 - 27% of patients fail to adequately synchronize
 - Actuation >1 sec. prior to inhalation results in a 90% reduction in inhaled mass
- Exhalation to residual volume⁴
- Failure to hold breath following inhalation⁵

⁴ Lavorini, F. *et al.* 2008. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respiratory Medicine* 102(4):593-604.

⁵ Melani, A.S. *et al.* 2004. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Annals of Allergy, Asthma & Immunology* 93(5):439-446.

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Specific Problems

- Inhalation rate too rapid⁶
- Inadequate shaking
 - Respirable dose reduced by > 35%⁷
- Other
 - Head tilt, less than full inhalation, insufficient wait time between actuations
 - Failure to prime, inadequate cleaning, multiple actuations

⁶ Molimard, M *et al.* 2003. Assessment of Handling of Inhaler Devices in Real Life: An observational Study in 3811 Patients in Primary Care. *Journal of Aerosol Medicine* 16(3):249-254.

⁷ Everard, M.L. 1995. Factors affecting total and respirable dose delivered by a Salbutamol MDI. *Thorax* 50(7):746-749.

Solutions Training

- But ...
 - A substantial proportion of health care professionals can not properly use an MDI⁸
 - Compliance = competence + adherence
 - "...many subjects appear competent (are able to use the device effectively) but contrive to use the device in a sub-optimal way in routine use."⁹

⁸ Crompton, G.K. *et al.* 2006. The need to improve inhalation technique in Europe: A report from the Aerosol Drug Management Improvement Team. *Respiratory Medicine* 100(9): 1479-1494.

⁹ Brennan, V.K. *et al.* 2005. True device compliance, the need to consider both competence and contrivance. *Respiratory Medicine* 99(1): 97-102.

Solutions

- Testing/Training
- Better labeling – pictograms
- Electronic monitoring to measure adherence¹⁰
- Spacers/Valved Holding Chambers (VHC)
 - Visible flow indicator
 - Audible flow indicator
 - Attractive design (children)

¹⁰ Apter, A.J. 2001. Testing the reliability of old and new features of a new electronic monitor for metered dose inhalers. *Annals of Allergy Asthma & Immunology* 86(4):421-424.

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Solutions

- Develop better understanding of formulation and device factors influencing product performance
 - QC Tests
 - Comparison Tests
 - Tests to assess product taste and feel

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Additional References

- Mitchell J.P. and Nagel M.W. 2009. Oral inhalation therapy: meeting the challenge of developing more patient-appropriate devices. *Expert Review of Medical Devices* 6(2): 147-155.
- Cipolla D. *et al.* 2010. Personalizing aerosol medicine: development of a delivery system tailored to the individual. *Therapeutic Delivery* 1(5): 1-16

Areas of Current Study at DPA

- Chlorofluorocarbon (CFC) vs. Hydrofluoroalkane (HFA) propellants
- Spacers/VHCs
- Shaking
- Nasal Actuation
 - Effects assessed
 - Parameters measured

Development of methods to characterize differences between CFC- and HFA-formulated MDIs

- Montreal accord may help restore ozone layer
 - EPA called for a gradual decrease of CFC production in the early 1990s
 - timeline for elimination of albuterol MDIs using CFCs was extended by FDA because of the lack of alternative products
 - While other propellants could easily be substituted for nonmedical uses of CFCs, this “essential use” exemption stems from the fact that manufacturers have had difficulty developing new propellants for use in MDIs.
 - FDA has waited for there to be more than one non-CFC alternative for each moiety before proposing to ban that particular CFC MDI.

Typical complaints contrast a “new” HFA product with the patient’s “old” CFC product and are related to **Taste or Feel**

- HFA inhalers require more frequent cleaning
- Between Oct. 15, 2008 and Feb. 26, 2010, there were nearly 400 complaints to FDA just re. one HFA product
 - More than 20% of these directly indicate some sort of device failure
 - Approximately 50% specify decreased drug effect or drug ineffective (could be medical, could be device-related)
- Many complaints for no or reduced # doses

Samples Selected for Study at DPA

Product	Active(s)	Propellant(s)	patient (µg)	Actuations per Canister	Manufacturer
Aerobid Inhale	Flunisolide	CCl2F2 C2Cl2F4 CCl3F	250	100	Forest Pharma.
Albuterol Inhaler	Albuterol	CCl2F2 CCl3F	90	200	Armstrong Pharma.
Azmacort	Triamcinolone Acetonide	CCl2F2	75	240	Kos Pharma.
Combivent	Ipratropium Bromide;	CCl2F2 C2Cl2F4	18	200	Boehringer Ingelheim
	Albuterol Sulfate	CCl3F	103		
Maxair Autohaler	Pirbuterol Acetate	CCl2F2 CCl3F	200	400	3M Pharma.
Advair HFA	Fluticasone Propionate; Salmeterol	CF3CH2F	45 21	120	Glaxo Grp.
Atrovent HFA	Ipratropium Bromide	CF3CH2F	17	200	Boehringer Ingelheim
Flovent HFA	Fluticasone Propionate	CF3CH2F	110	120	Glaxo Grp.
Proair HFA	Albuterol Sulfate	CF3CH2F	108	200	Teva
Provental HFA	Albuterol Sulfate	CF3CH2F	108	200	3M Pharma.

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Effects Examined (Example: Proair)

- Cleaning
 - Maximum interval (based on patient instructions) vs. 200% of that value (if possible)
 - Dose (#sprays): 1-2
 - Dose per day: 4-6
 - Cleaning frequency: once per week
 - Maximum interval = 2 spray/dose * 6 dose/day * 7 day = 84 sprays (short cleaning interval)
 - Long cleaning interval = 158 sprays
- Delay between actuations
- Canister life stage

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Metrics

- Plume Ovality (SprayVIEW)
- Plume (SP) Area (SprayVIEW)
- Impaction Force (TA.XT+)
- Total Drug Delivered
(Andersen Cascade Impactor, ACI)
- Fine particle fraction (ACI stages 3, 4 & 5)
- Orifice diameter (Keyence VHX-500)

Purpose is to establish metrics that will show differences between HFA and CFC products in order to provide better instructions to health-care providers.



CFC- / HFA-MDI Study Expected Outcomes

- Provide additional guidance to CDER reviewers regarding important patient use factors and expected product performance re. differences between these two types of MDIs.
 - Are some patient observations only perceived vs. actual?
 - Are there actual problems with product use and/or instructions?

Evaluation of the effect of spacers on the *in vitro* performance of orally inhaled drug products

- Spacer devices serve as holding chambers for the aerosol plume of metered dose inhaler (MDI) drug products.
- Often used for young children who cannot coordinate inhalation with inhaler actuation.
- Multiple factors such as geometry, humidity (static charge), product formulation, and MDI valve/actuator design can alter the respirable dose.

Spacers/VHCs

- Need to understand these factors and their interactions better so that *in vitro* testing adequately represents the effects of these add-on devices on drug delivery.
 - Provide better recommendations for health-care providers re. age appropriate spacer devices for use with specific MDIs for pediatric patients.
 - Provide better recommendations for CDER reviewers and MDI sponsors regarding appropriate testing to be done for use of MDIs and spacer devices in the pediatric population.



Products Examined

- MDIs
 - Flovent HFA (Fluticasone Propionate)
 - Proventil HFA (Albuterol Sulfate)
 - QVAR (Beclomethasone Dipropionate)
- Spacers (Valved Holding Chambers, VHC)
 - AeroChamber Plus
 - Optichamber Advantage
 - Others



What and How

- Effects examined
 - Delay between actuation and inhalation
 - Inhalation flow rate
 - Cleaning
 - Static charge
- Metrics
 - Total drug delivered
 - Aerodynamic Particle Size Distribution – Mass Median Aerodynamic Diameter
 - Fine particle fraction ($< 5 \mu\text{m}$)

Additional Studies

- Design of Experiment Modeling and In Vitro Testing of Nasal Sprays Based on Usage Ergonomics
 - develop a better understanding of the relationship range of human usage parameters for nasal spray products by measuring the actuation profiles of trained adult testers using commercial nasal spray pumps filled with synthetic aqueous formulations with controlled amounts of viscosity and/or surface tension altering additives.¹²

¹² Guo, C. *et al.* 2008 Assessment of the Influence Factor on In Vitro Testing of Nasal Sprays Using Box-Behnken Experimental Design. *Eur. J. Pharm Sci*, 35(5): 417-426.

Additional Studies

(Nasal spray actuation – continued)

- Parameters
 - Actuation force
 - Solution viscosity
 - Solution surface tension
- Metrics
 - Shot weight
 - Spray pattern
 - Plume geometry
 - Droplet size distribution



Additional Studies

- Effect of shaking on MDI performance
 - In planning stage



Expected Outcomes of Research

- Better understanding of factors influencing performance of these complex dosage forms
- Better understanding of consequences of patient misuse
- Better ways to measure or predict compliance
 - Better *in vitro* tests
 - New *in vitro* tests



Acknowledgements

- DPA Inhalation Laboratory staff
 - Changning Guo
 - Xiaofei Liu
 - Kim Story
 - Diem (Cindy) Ngo
 - Sara Hadwiger
 - Shafiq Ahadi
- Cindy Buhse, Director DPA
- CDER Regulatory Science and Review Enhancement Program
- FDA Critical Path Program