Inhaled Product Advances for Aerosolization, Breath Coordination and Patient Monitoring

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Biography and Contact Information

- Design and characterization of traditional and novel inhaled drug products
  - Small pharma, CRO, academia
  - Nebulization and dry powder inhalation
- Patient use testing and device design control

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Let’s start with the most obvious statement of the day...

Medication that isn't taken properly cannot benefit the patient. May not could harm.
Regulatory Considerations for Inhalers

Nebulizer $\rightarrow$ 510k* or NDA

DPI/MDI $\rightarrow$ NDA

*CDRH may not require 510k if drug-specific device
Regulatory Classification

Chipperfield and Chesworth, Regulatory Rapporteur – Vol 15, No 5, 2018
FDA Device Review

- Appropriateness for user, environment
- Cascade Impaction
- Delivered Dose
- Particulate matter, VOC
- Category (ISO 10993), E/L
- Firmware counts
- Does not apply to manufacturing process
- Formative/Summative testing
- Communicate plan to FDA
- ANSI/AAMI ES60601-1 (General)
- IEC 60601-1-2 (Tests)
Avoidable Medical Cost

• Of the 213B, 105B is due to nonadherence
  • Others are delayed treatment, antibiotic misuse, medical error
• 55% of asthma patients do not take their medication correctly

IMS Institute 2013, Avoidable Cost in US healthcare
Nonadherence to Inhaled Medication

Only 30% of patients performed a successful first inhalation

96% self-reported correct technique

61% of patients don’t read the IFU

Baker 2018, Realistic Pulmonary Delivery System Trainers, ON drug Delivery, April 16, 2018, no 85, p28
The Cause of Nonadherence

- Device misuse
- Improper breathing
- Device malfunction
- Non-use
- Incorrect Dose

- Simple operation
- Correct Dose
- Patient reminders
- Robust design

- Regulatory guidance
- Technology advance
- User focused design

Design and instruction
So what’s being done?

- Patient Monitoring
- Patient Coordination
- Aerosol Technology
Patient Monitoring – Add-on Devices

Add-on Companies

- Adherium
- Propeller Health
- Teva (formerly Gecko)
- CapMedic
- Biocorp Inspair
- Cohero Health

Hailie (by Adherium) for Symbicort HFA

www.hailie.com/products/smarttouch-symbicort-non-rechargeable
COPD patients studies for rescue inhaler (albuterol) use

- During exacerbations 15% increase in rescue inhaler use
- Could not predict mild exacerbations

Exacerbation and hospitalization

Patient Monitoring – Smart Devices

Vibrating mesh neb
• Disinfectable
• Controls breathing rate, profile
• Bree Connect™ tracks inhalations, time, reminds of missed dose
• Bluetooth connected

Patient Monitoring – Clinical Studies

- Adherence and efficacy (lung function) can be monitored
- Encrypted and available for study coordinators
- Alternative to patient diaries
- Patient knowledge of system improves adherence
Patient Monitoring – DPIs

Inhalers are noisy
• Using a microphone of smart device and software/algorithm can be used for patient monitoring

No add-on needed for monitoring

Each DPI has a unique acoustic signature
• Can identify the device
• Can determine flow rate
• Can detect open/close, actuation and drug emission

Figure 1: Frequency response plots for Sun Phama's Stairhaler DPI.
Breath Coordination – DPI and nebulizers

Open-Inhale-Close DPI Devices

Dose preparation errors may be reduced to as low as 1%

Breath Actuated Liquid Aerosols

Vectura: Akita System (right) controls ariflow, synchronizes nebulization. Dance: The Dance 501 nebulizer (left) senses breath profile uses a vibrating mesh to synchronize insulin aerosol with inhalation


Knowles 2018, Meeting future needs of respiratory drug dev, ON drug Delivery, April 16, 2018, no 85, p10

https://www.dancebiopharm.com/
http://www.akita-jet.com/

SAVARA
Breath Coordination – pMDIs

3M Intelligent Control Inhaler

Patient coordination
• Breath-actuation
• Flow regulation
• On-screen instructions

Patient Monitoring
• Reminds and provides patient feedback
• Records and stores use data
• Bluetooth link to smartphone


Breath Actuated Metered Dose Inhalers

http://synchrobreathe.co.za/
http://hcp.qvar.com/dosing.aspx
Aerosol Generation – Liquid

**Soft Mist**
- Colliding jets
- Capillary
- Cartridge containing drug solution
- Uniblock
- Filter

**Vibrating Mesh**

**In Development**
- Surface Acoustic Wave (SAW) aerosolization
- Capillary Aerosolization
- Electrohydrodynamic atomization

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Carvalho 2016, J Pharmacy and Pharmacology v68 p558
Scherer 2010, J Pharm Sci v100, 1, p 98
Watts 2008, Drug Delivery and Industrial Pharmacy, v34 p913
Aerosol Generation – Powder

Thermal Aerosol

- Staccato – inhaled thermal aerosol, creates vapor that condenses into aerosol
- ½ second of heat, minimal degradation
- Approved for schizophrenia/bipolar disorder

“Active” DPI

Adamis 4000 (3M Taper)- API layered onto microstructured tape, dispersed with impactor

Teva (formerly MicroDose) piezo driven DPI aerosolizes from pierced blister

https://www.alexza.com/staccato/staccato-platform
http://www.adamispharmaceuticals.com/pipeline/apc-4000/
Future Direction

- Clinical evidence of patient benefit
- Payers cover more smart devices
- Regulators begin to require “smart” features

Questions?