

# Inhaled Product Advances for Aerosolization, Breath Coordination and Patient Monitoring

April 9, 2019

Alan Watts, PhD

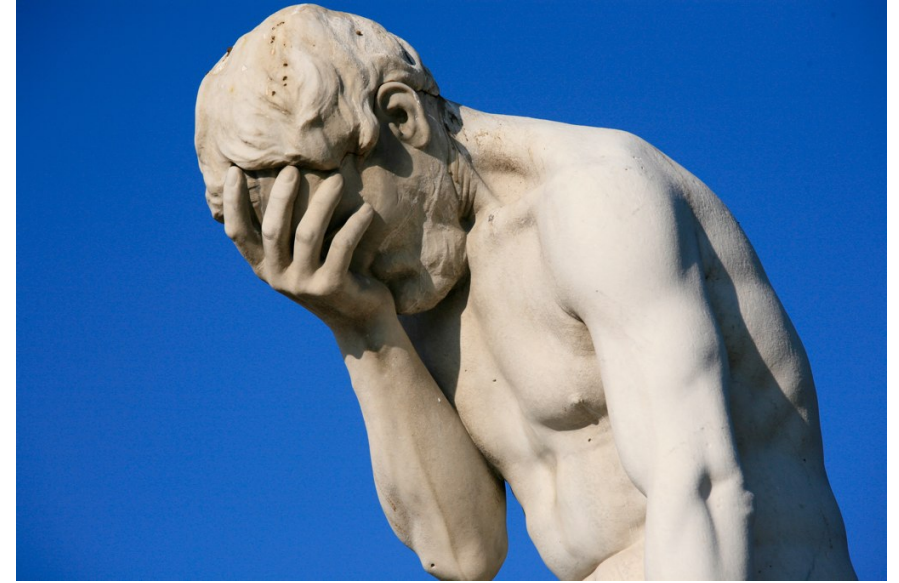
Senior Scientist, Savara Pharmaceuticals



# 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
- Email: [alan.watts@savarapharma.com](mailto:alan.watts@savarapharma.com)

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 → 510k\* or NDA



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

DPI/MDI → NDA





# Regulatory Classification

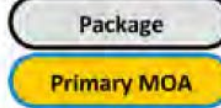
## Combining products

## USA

## EU

1		<b>Combination Product</b> (Single-entity), CD/BER (+CDRH)	<b>Medicinal Product</b> (single integral-combined-nonreusable), CA <sup>†</sup> , No CE-mark
2		<b>Combination Product</b> (Single-entity), CDRH (+CD/BER)	<b>Medical Device</b> with ancillary substance, NB <sup>††</sup> , Class III, CE-mark
3		<b>Combination Product</b> (Packaged together), CD/BER (+CDRH)	<b>Medicinal Product</b> Medical Device, CE-mark
4		<b>Combination Product</b> (Packaged together), CDRH (+CD/BER)	<b>Medical Device, CE-mark</b> Medicinal Product
5		<b>Combination Product<sup>†††</sup></b> (Cross-labelled), CD/BER + CDRH	<b>Medicinal Product</b> <b>Medical Device, CE-mark</b>
6		<b>Convenience Kit</b> 510(k)/PMA Medical Devices	<b>Procedure/System Pack</b> of CE-marked Medical Devices
7		<b>'Fixed dose' Combination Product</b>	<b>Medicinal Product or Medicinal Products</b>

Legend:

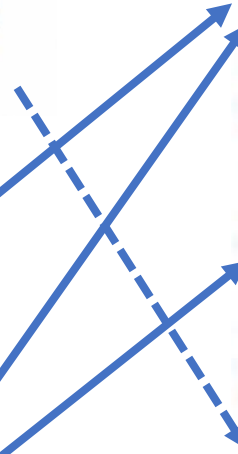
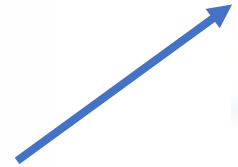


**Drug\*** = Drug or biologic, for the purposes of this image

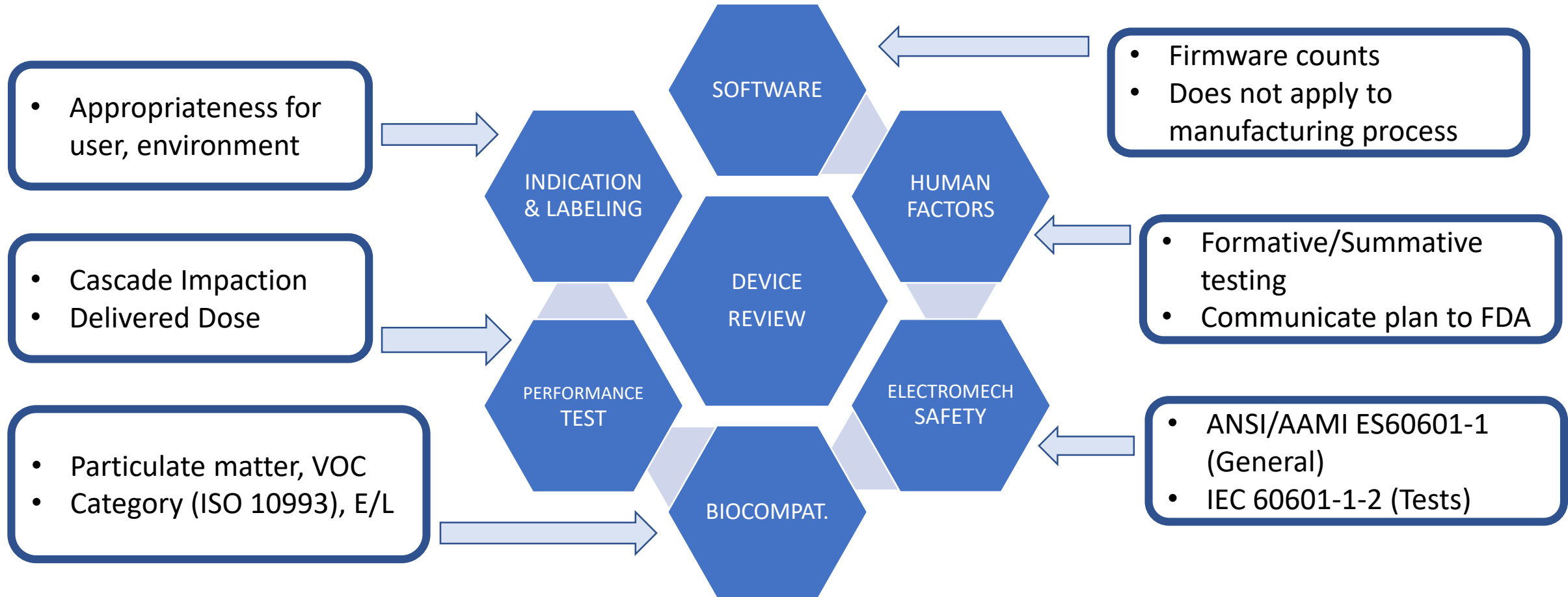
**†** = Opinion from Notified Body (under MDR), Confirmation by Applicant (under MDD)

**††** = Scientific Opinion from Competent Authority

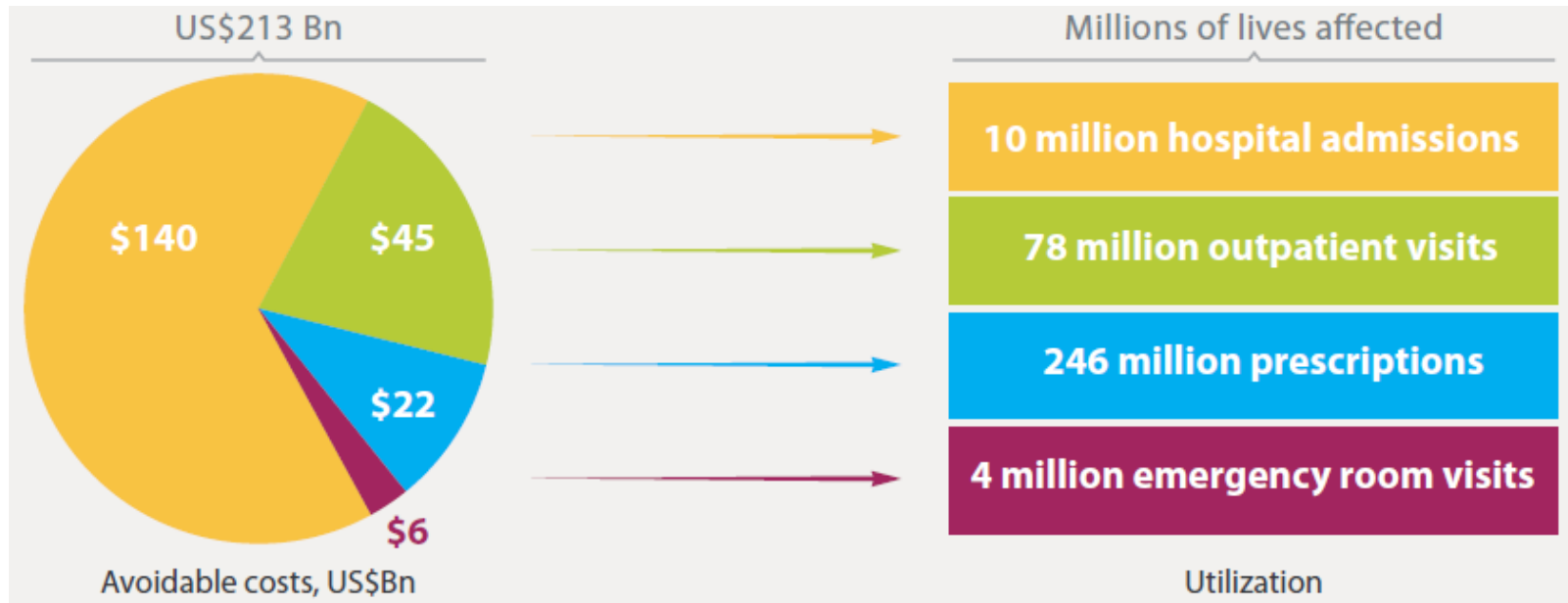
**†††** = Note, where a device refers to a drug, the FDA considers this a Device Referencing Drug (DRD), which may (or may not) also meet the current definition of a Combination Product.



# FDA Device Review



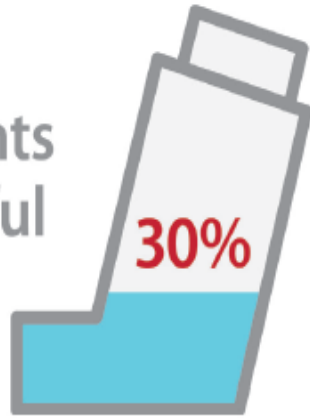
# Avoidable Medical Cost



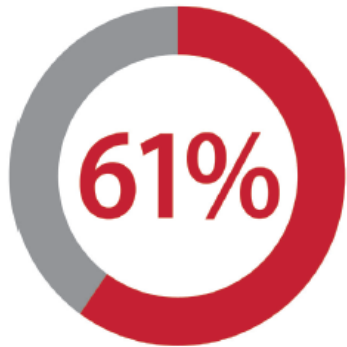
- Of the 213B, 105B is due to nonadherence
  - Others are delayed treatment, antibiotic misuse, medical error
- 55% of asthma patients do not take their medication correctly

# Nonadherence to Inhaled Medication

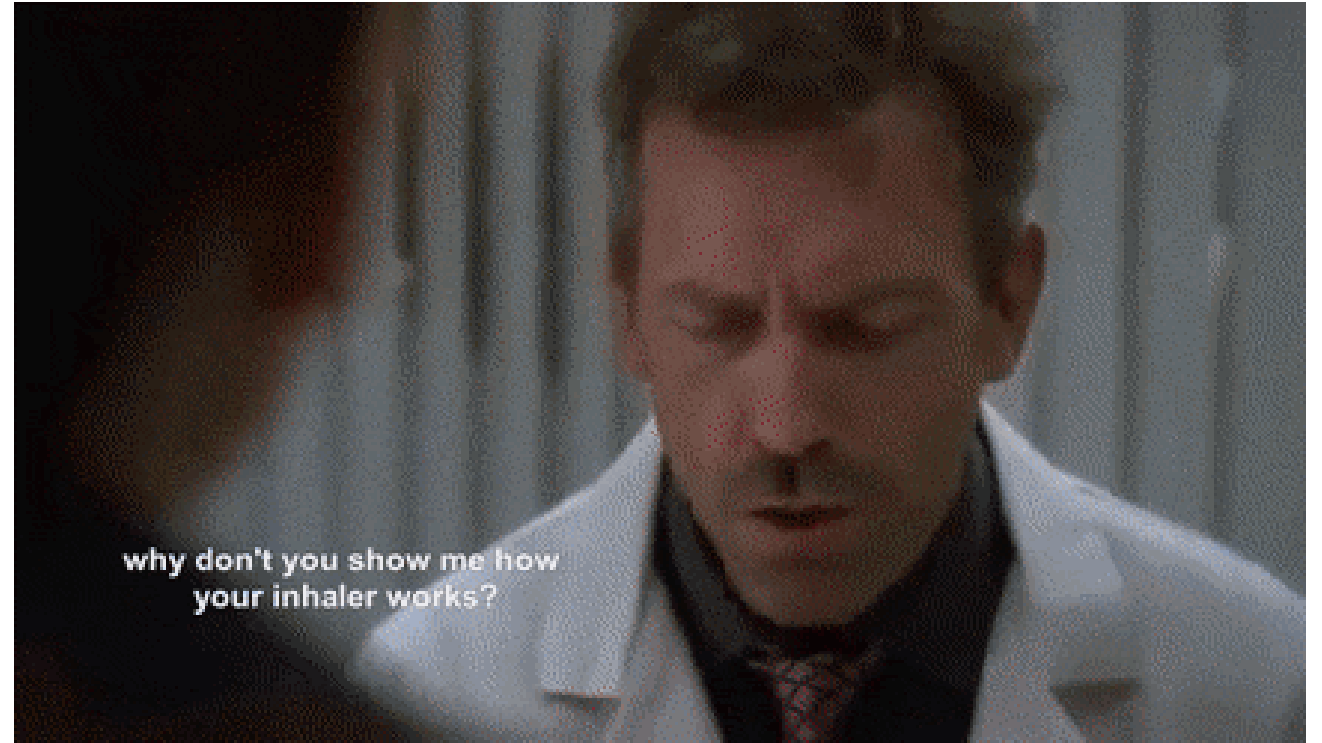
Only **30%** of patients performed a successful first inhalation



**96%** self-reported correct technique

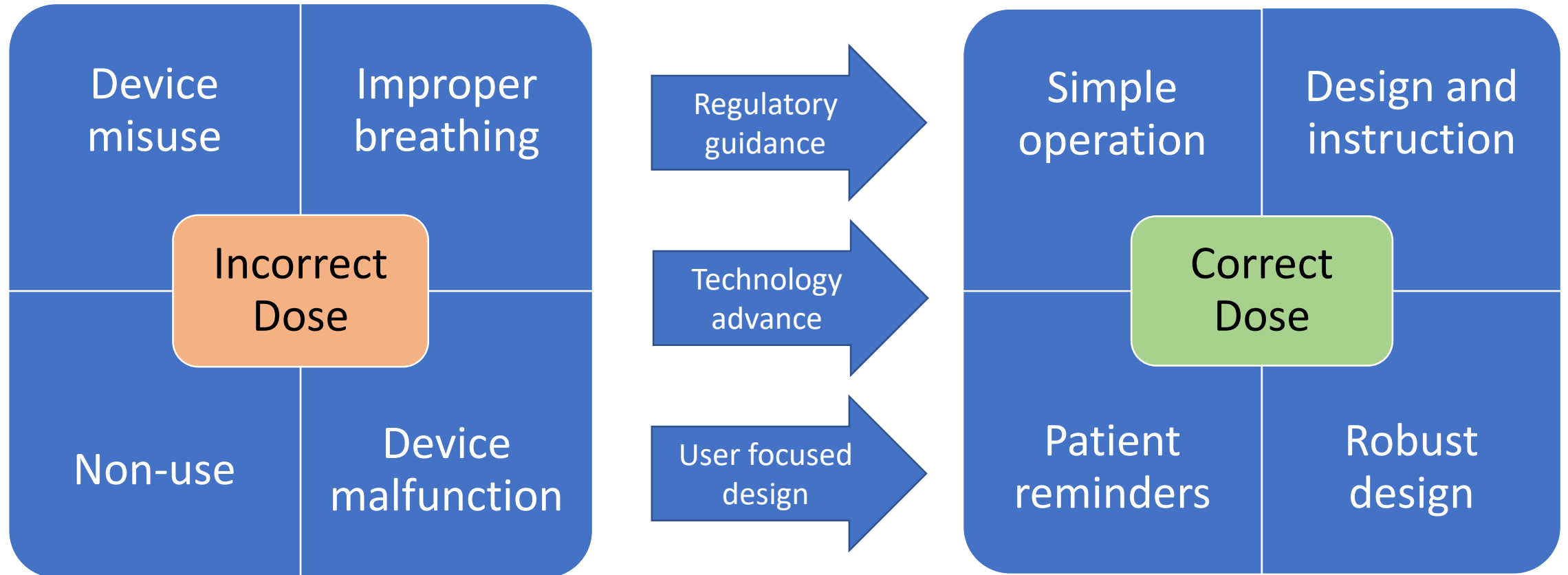


of patients don't read the IFU





# The Cause of Nonadherence



# So what's being done?

Patient  
Monitoring

Patient  
Coordination

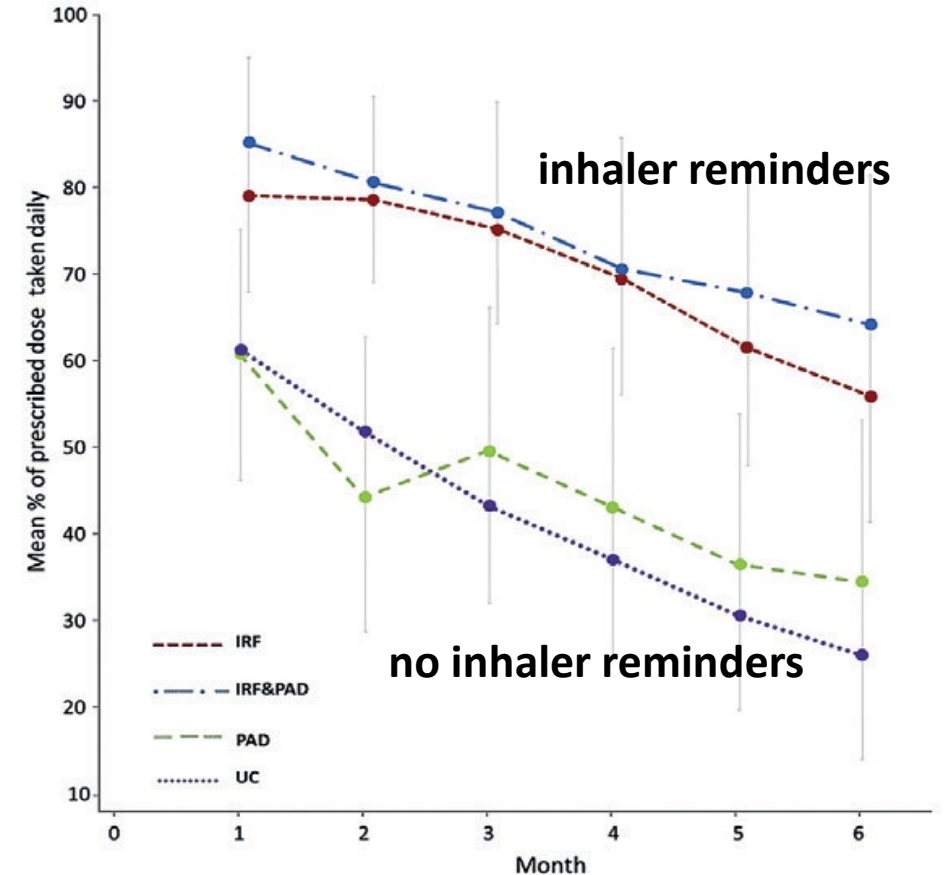
Aerosol  
Technology

# 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



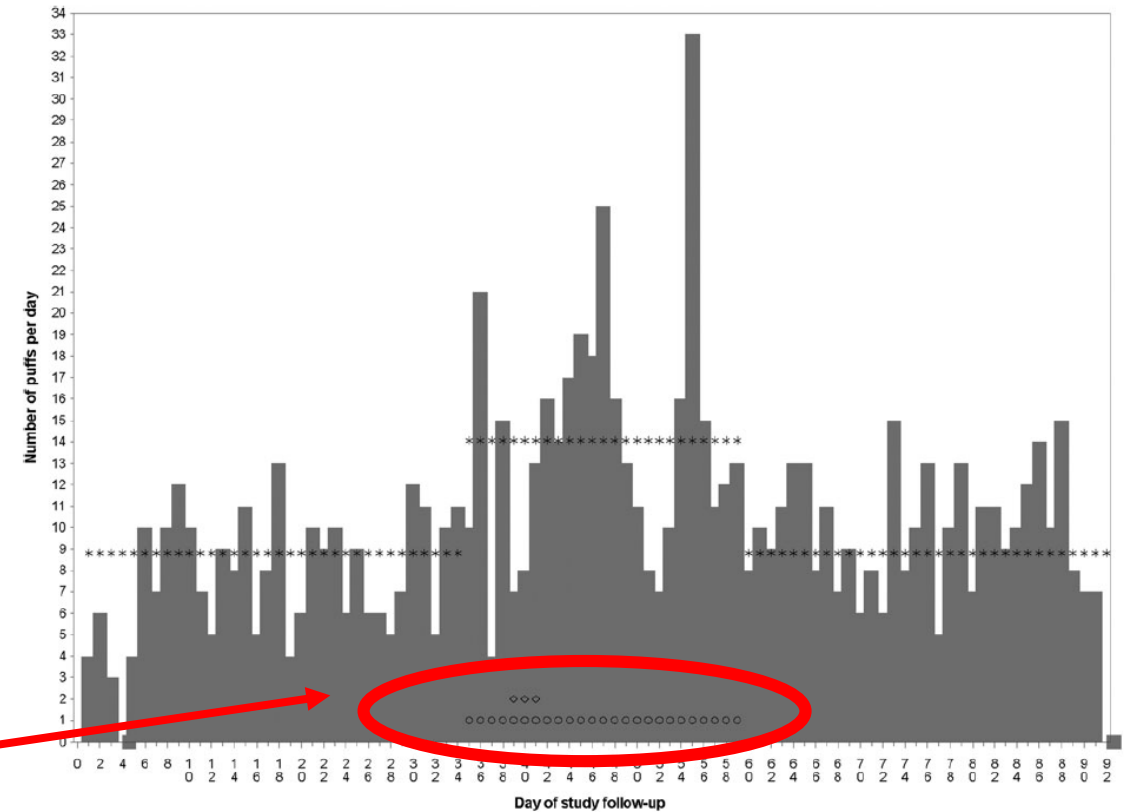
# Patient Monitoring – Add-on Devices

## Propeller Health



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

## Vectura Fox® - Breelib™

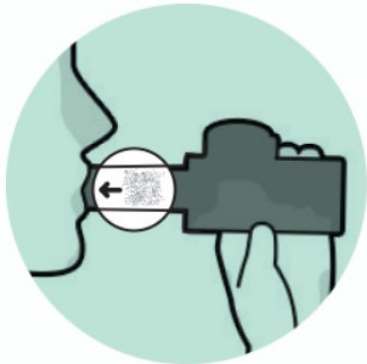


Vibrating mesh neb

- Disinfectable
- Controls breathing rate, profile
- Bree Connect™ tracks inhalations, time, reminds of missed dose
- Bluetooth connected

Breathe in...

...breathe out...



## Novartis Cloudhaler



## Presspart eMDI



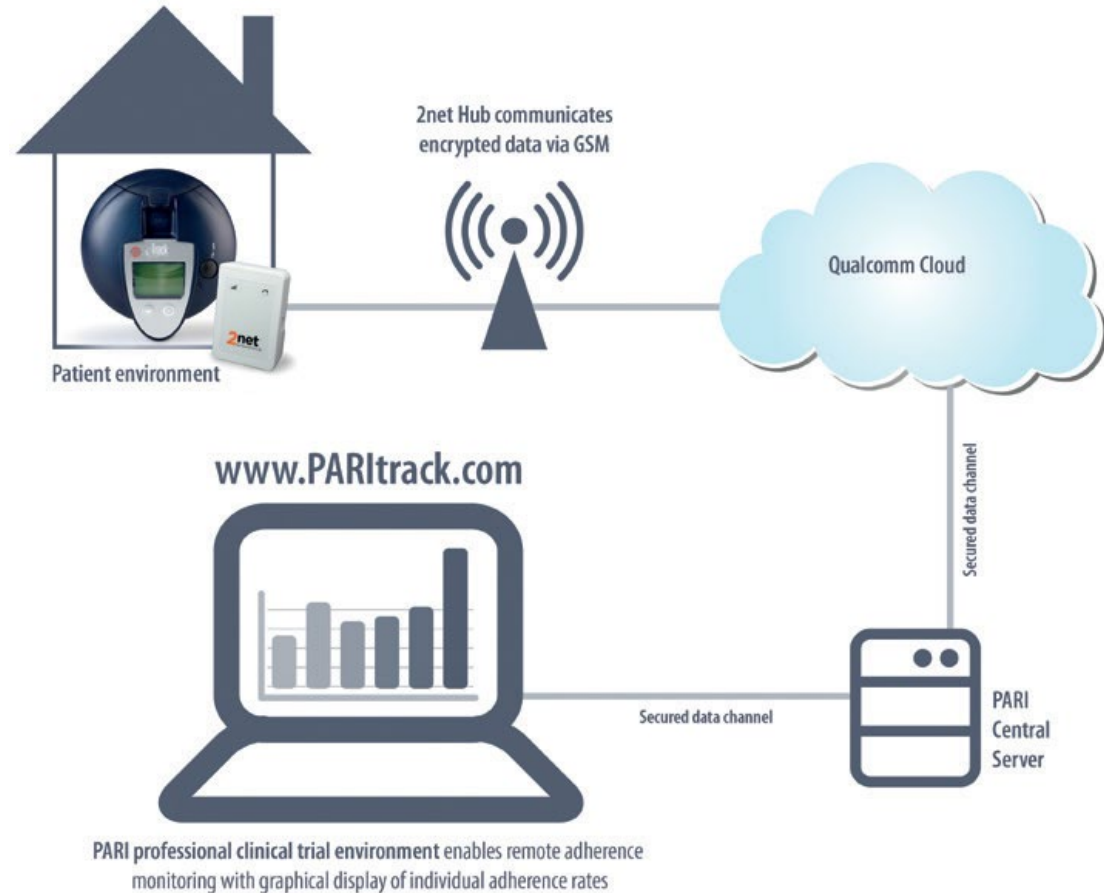
## Novartis USSC-03

<http://www.breelib.com/index.php?breelib=lib&lang=en>



# 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

## PA Consulting

Inhalers are noisy

- Using a microphone of smart device and software/algorithm can be used for patient monitoring

No add-on needed for monitoring

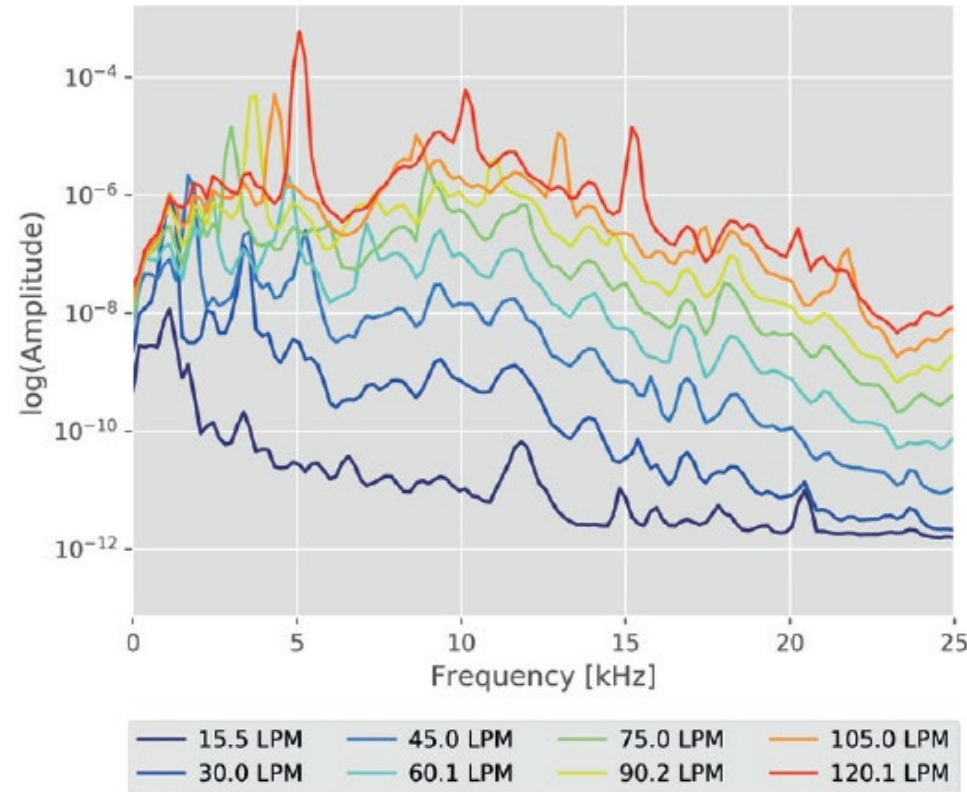
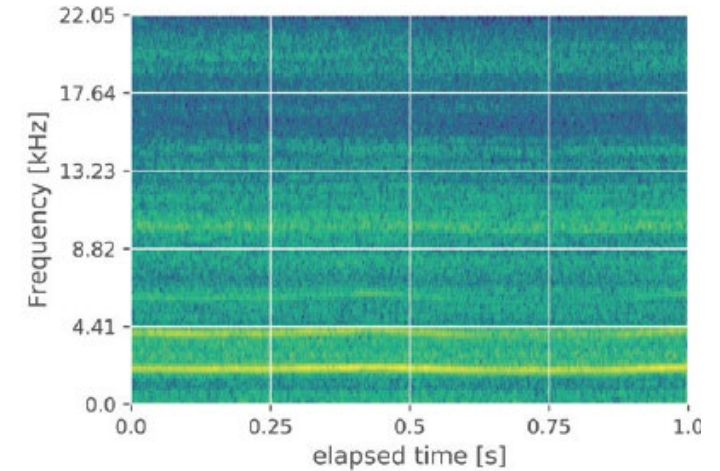


Figure 1: Frequency response plots for Sun Pharma's Starhaler DPI.



Each DPI has a unique acoustic signature

- Can identify the device
- Can determine flow rate
- Can detect open/close, actuation and drug emission

# Breath Coordination – DPI and nebulizers

## Open-Inhale-Close DPI Devices



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

<https://medicalxpress.com/news/2017-09-fda-oks-glaxo-inhale-combine.html>  
Knowles 2018, Meeting future needs of respiratory drug dev, ON drug Delivery, April 16, 2018, no 85, p10

## Breath Actuated Liquid Aerosols



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

Virchow JC, 2015, A review of the value of inhalers for COPD and asthma. *J Market Access Health Policy* 3: 28760

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

# 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



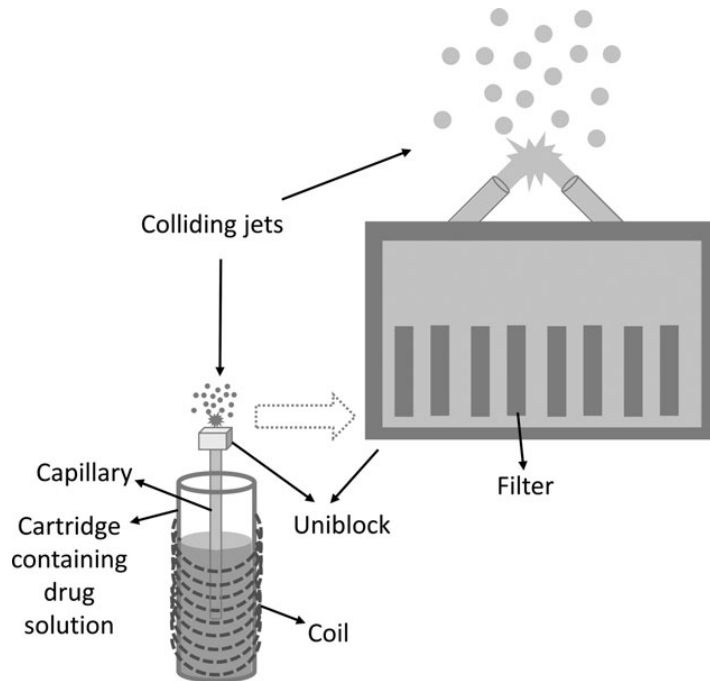
[https://www.3m.com/3M/en\\_US/drug-delivery-systems-us/technologies/inhalation/intelligentcontrol/](https://www.3m.com/3M/en_US/drug-delivery-systems-us/technologies/inhalation/intelligentcontrol/)

<http://synchrobreathe.co.za/>  
<http://hcp.qvar.com/dosing.aspx>

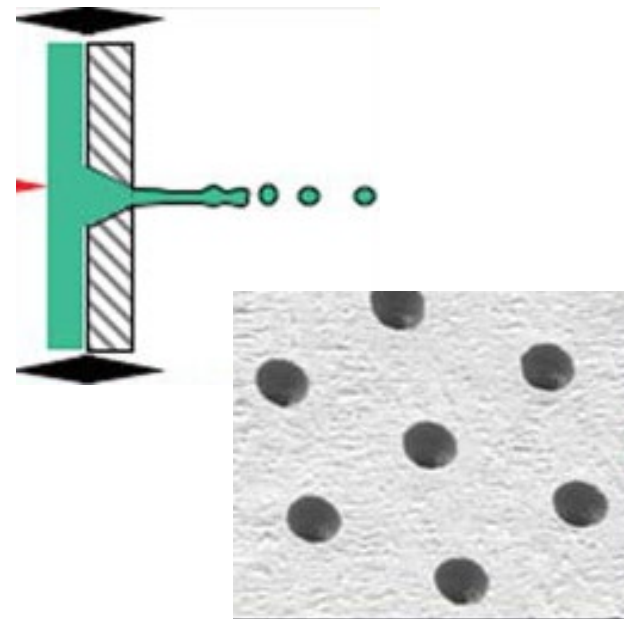


# Aerosol Generation – Liquid

## Soft Mist

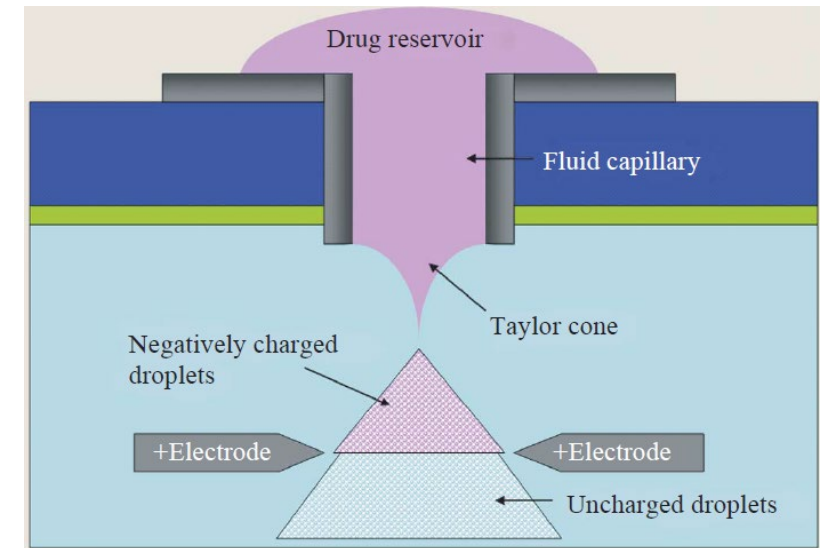


## Vibrating Mesh



## In Development

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

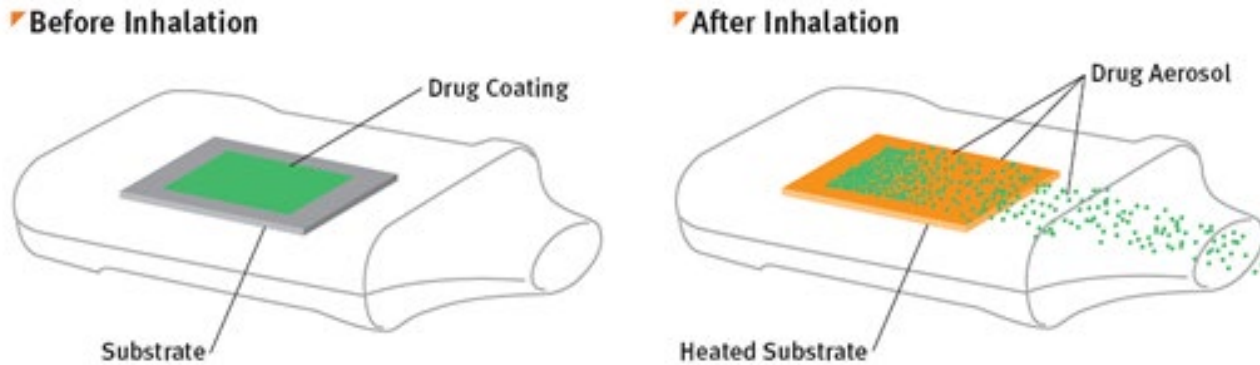


Carvalho 2016, J Pharmacy and Pharmacology v68 p558  
Scherer 2010, J Pharm Sci v100, 1, p 98  
Watts 2008, Drug Delivery and Industrial Pharmacy, v34 p913



# 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

<https://www.alexza.com/staccato/staccato-platform>

<http://www.adamispharmaceuticals.com/pipeline/apc-4000/>

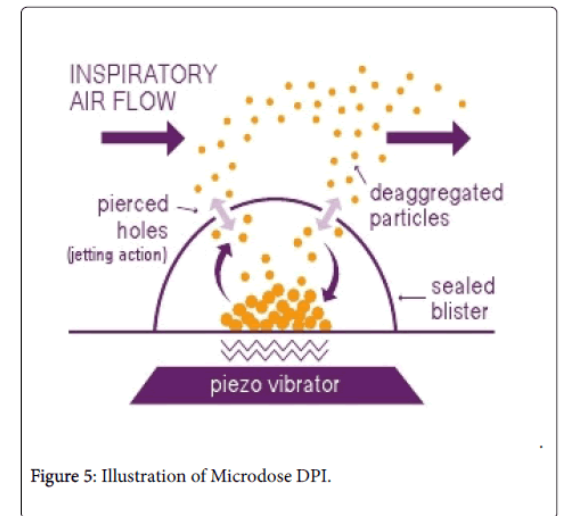
<https://www.omicsonline.org/open-access/dry-powder-inhaler-devices-2157-7013-1000271.pdf>

## “Active” DPI

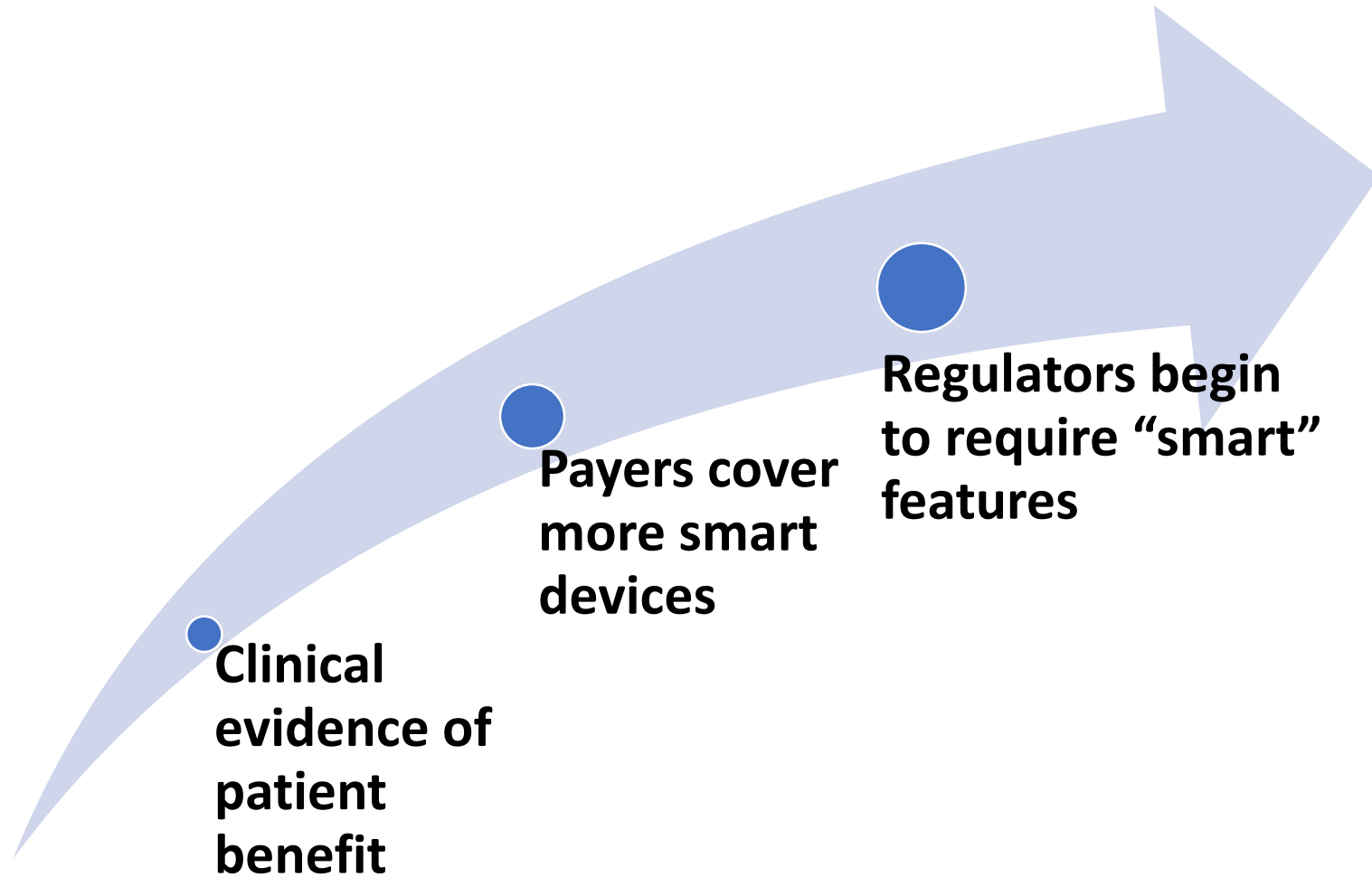


Adamis 4000 (3M Taper)- API layered onto microstructured tape, dispersed with impactor

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



# Future Direction



## Questions?

