Loxapine Inhalation Powder: OTR Research Conducted to Inform the PSG Recommendations

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 2: Noteworthy Guidances for Nasal Suspension and Inhalation Products

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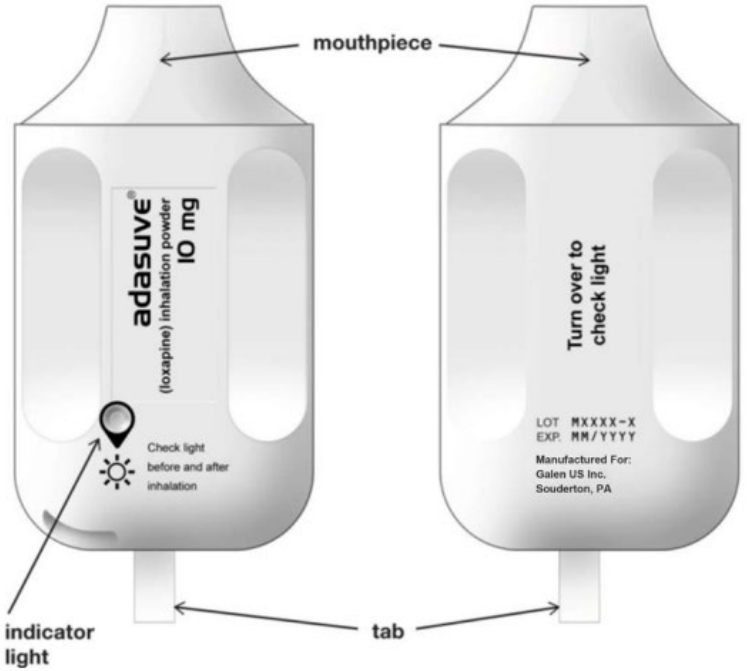
Learning Objectives

- Be familiar with the main features of the the drug product, **ADASUVE (Loxapine, 10 mg) Inhalation Powder**.
- Understand and describe the **research efforts** used to analyze the **aerosol properties** of ADASUVE.
- Understand and describe the recommendations within the **product-specific guidance (PSG) on *Loxapine Inhalation Powder***.

The Reference Listed Drug (RLD): ADASUVE

Loxapine (10 mg) Inhalation Powder[1,2,3]

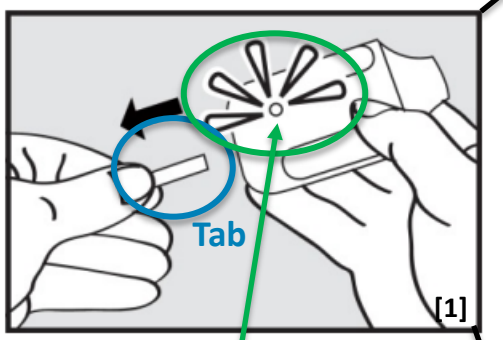
- **A single-use, drug-device combination product**
- **Indications and Usage:** atypical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults
- **Dosage & Administration:**
  - Must be administered by a healthcare professional in a certified healthcare setting only (available under a restricted program – **ADASUVE REMS**)
  - 10 mg by oral inhalation using an inhaler
  - Administer a single dose within any 24-hour period
  - Prior administration, screen patients for pulmonary disease/respiratory abnormalities



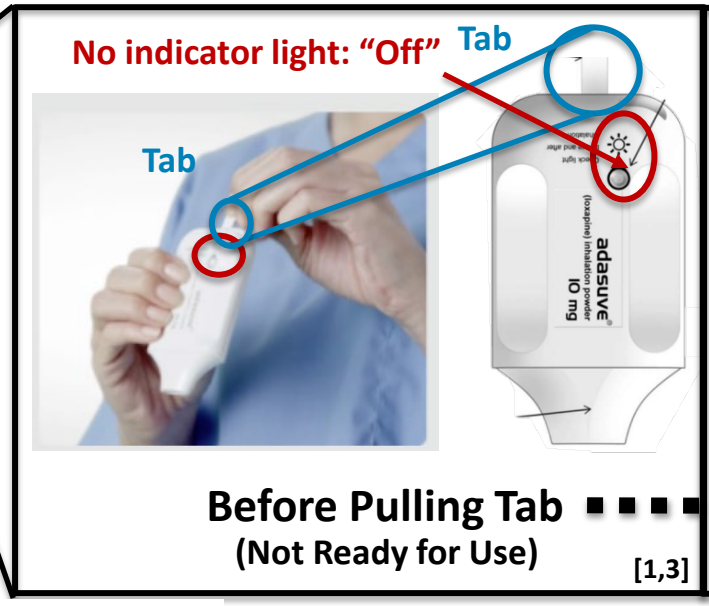
ADASUVE Administration

1. Open Pouch

2. Pull Tab

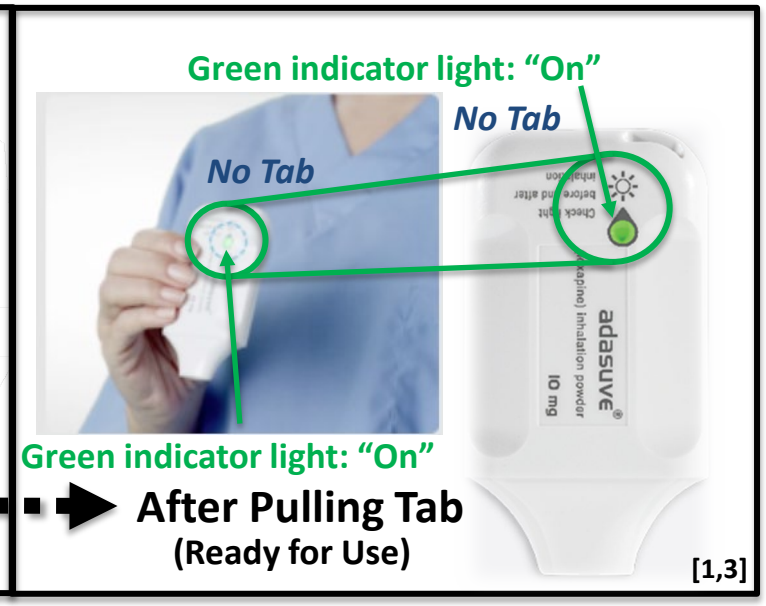


Green indicator light: "On"



Before Pulling Tab
(Not Ready for Use)

[1,3]

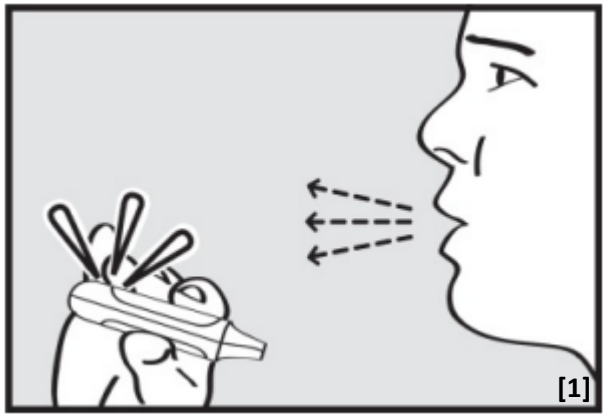


Green indicator light: "On"

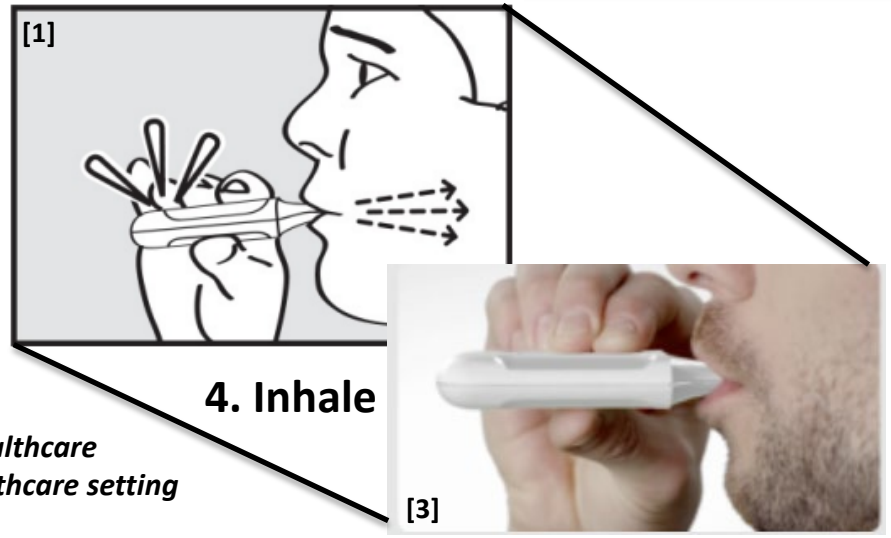
After Pulling Tab
(Ready for Use)

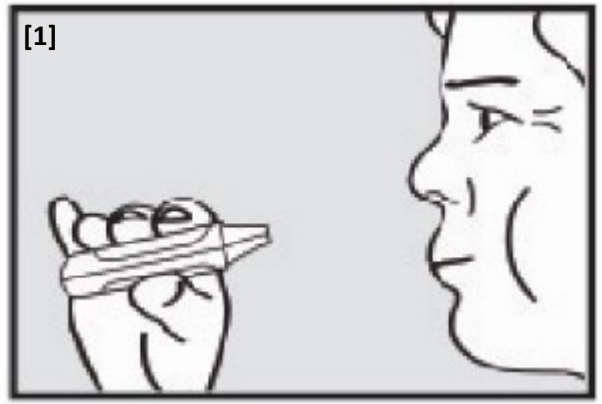
[1,3]

3. Exhale



4. Inhale





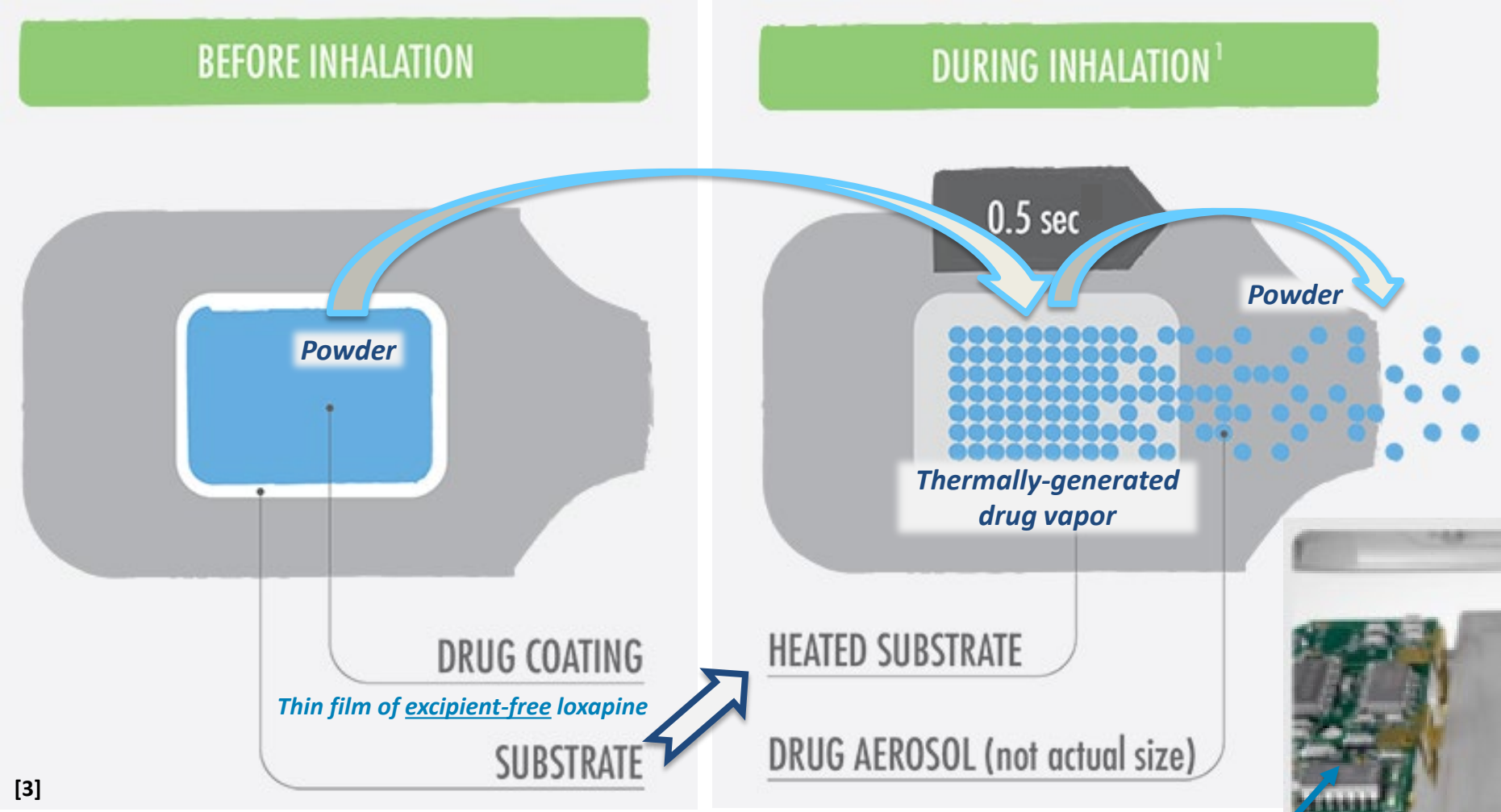
5. Hold Breath

Green indicator light "Off" = successful dosing

Must be administered by a healthcare professional in a certified healthcare setting only (ADASUVE REMS)

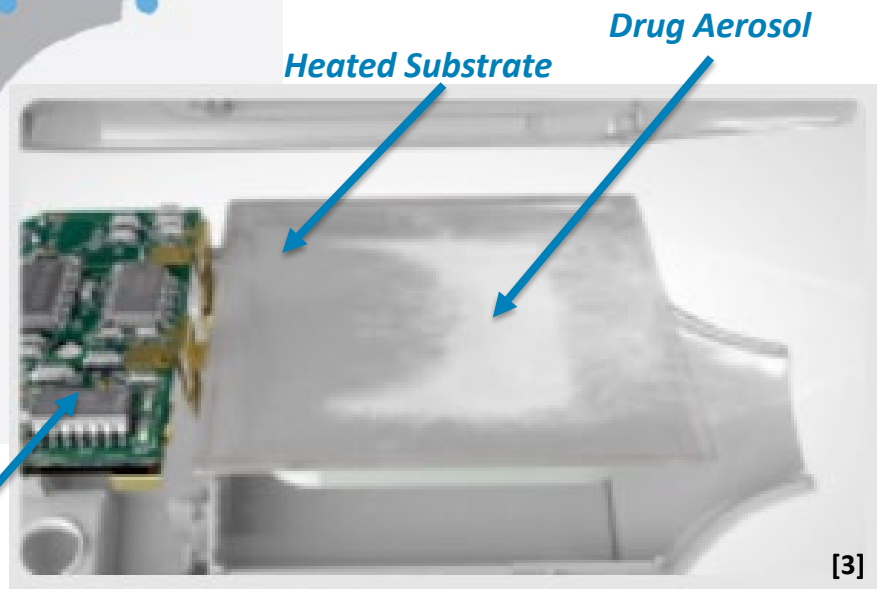
www.fda.gov

ADASUVE Delivery Mechanism



[3]

ADAUSVE:
Provides rapid systemic delivery of an aerosol of pure loxapine that is quickly absorbed through the lungs and into the bloodstream.



[3]

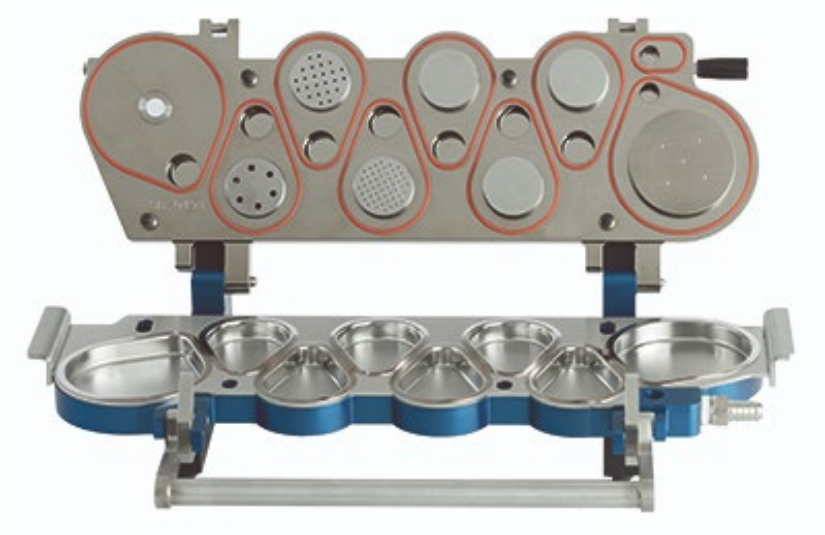
Oral inhalation initiated rapid heading of thin film

OTR Research Proposal

- Better understand the **critical quality attributes** of ADASUVE
  - **Unique** **thermally generated aerosol** process
    - Differs from other inhalation powder drug products (Dry Powder Inhalers) → **blended API/Excipient powder flow** and **deaggregation** process
- Impact of **inspiratory flow** on ADASUVE performance
- **Laser diffraction** as **alternative method** to measure **drug particle size distribution (PSD)** compared to conventional **aerodynamic particle size distribution (APSD)**
  - **ADASUVE is an excipient-free, drug-device combination**

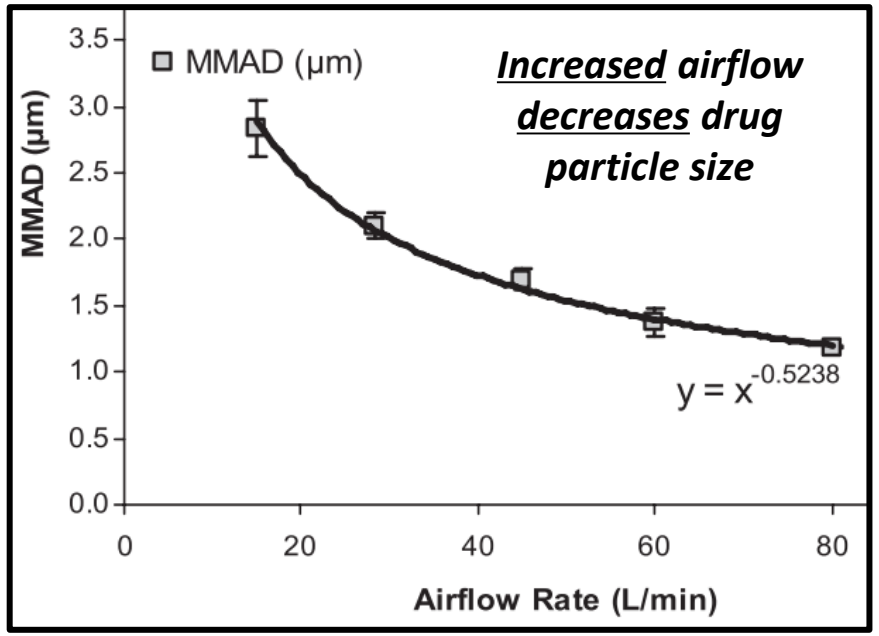
ADASUVE Aerodynamic PSD

(predict amount of drug deposited within the lungs in different regions based on aerodynamic size)



Next Generation Impactor (NGI) Data

- Aerodynamic particle size distribution (**APSD**)
- Mass median aerodynamic diameter (**MMAD**)
- Geometric standard deviation (**GSD**)
- Fine particle mass (**FPM**)

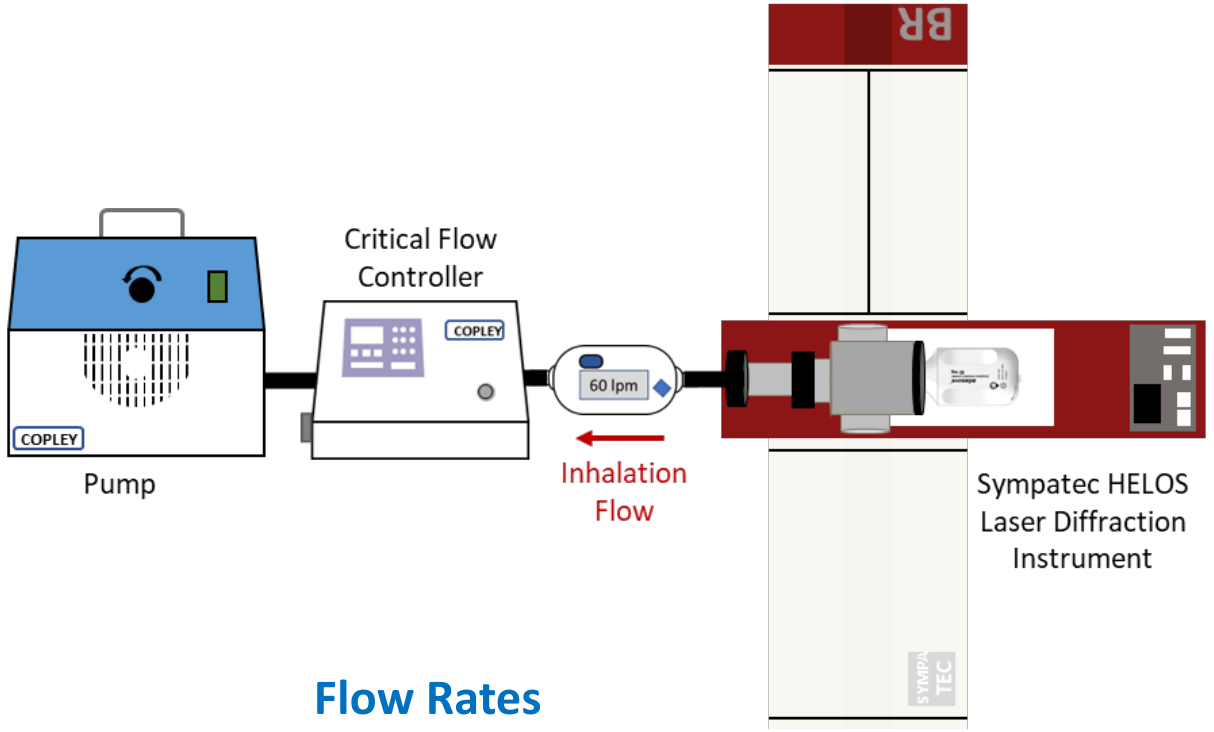


MMAD vs. airflow rate as measured by NGI.[5]

ADASUVE Laser Diffraction (LD)

Research Goals

- Alternative method to measure PSD
- LD measures the volume weighted PSD of the active pharmaceutical ingredient, since ADASUVE is excipient-free
- Determine the effect of inspiratory flow on PSD
- Note: LD does not determine particle morphology



Flow Rates

15, 28.3, 60, 90 LPM

Particle Measurement Range

0.5 to 175 µm

Inhalation Profile

Fixed Flow Rate, Fixed Volume (4 Liters)

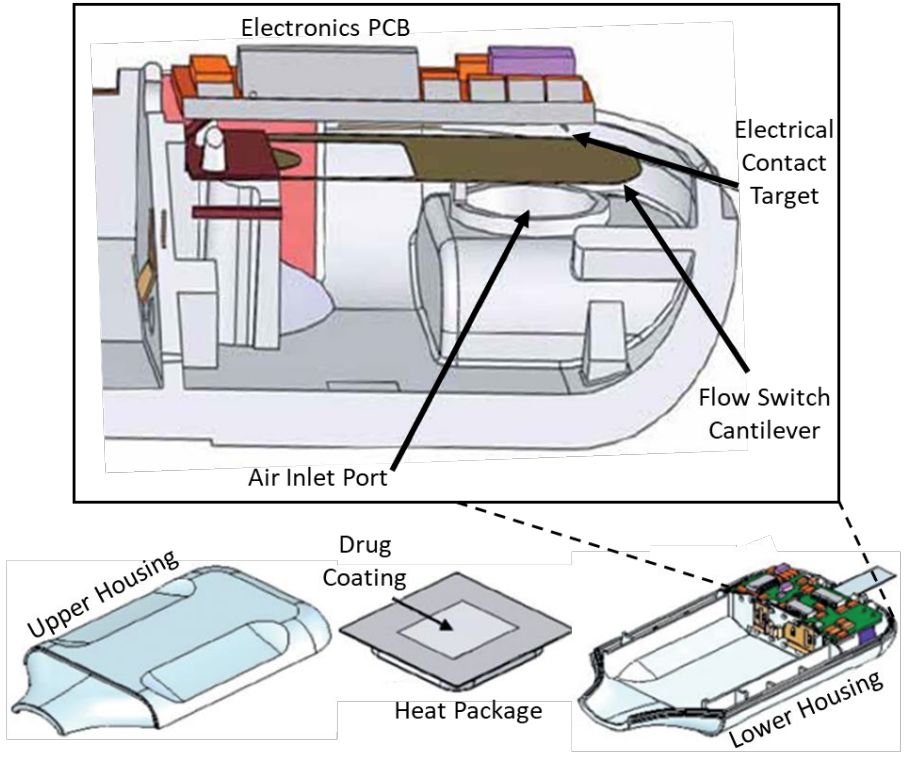
Determining Lowest Actuation Flow Rate

Actuation Flow rate (LPM)

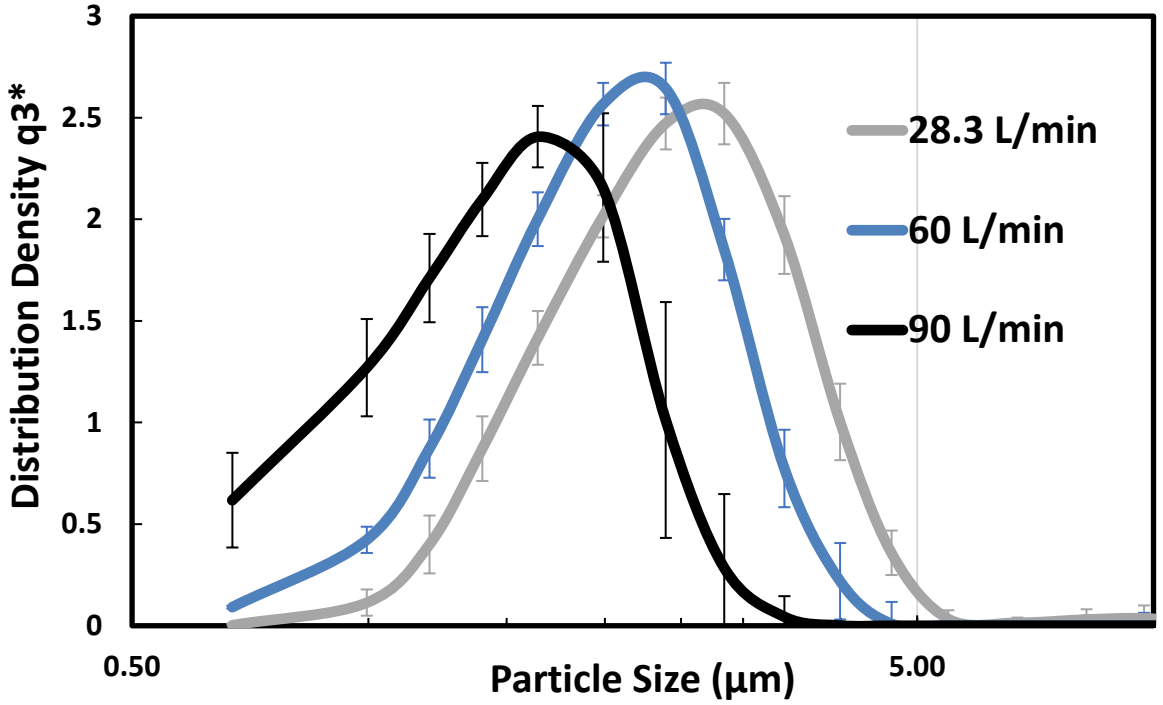
	15	16	17	18	19	20	21
Sample 1	Failed	Failed	Failed	Failed	Failed	Actuated	
Sample 2	Failed	Failed	Failed	Failed	Failed	Failed	Actuated
Sample 3	Failed	Failed	Failed	Failed	Actuated		

- To better understand the device capabilities, we examined the minimum flow rate needed to trigger the flow sensor used to activate the device
- Lower flow rates were examined until device actuation occurred
- Each flow rate increment (+1.0 L/min) was tested until actuation
- Studies demonstrated that the device failed to actuate at 15 L/min – 18 L/min
- Average minimum actuation flow rate of 20 L/min (+/- 1 L/min)

Cross-section of a Adasuve Flow Sensor

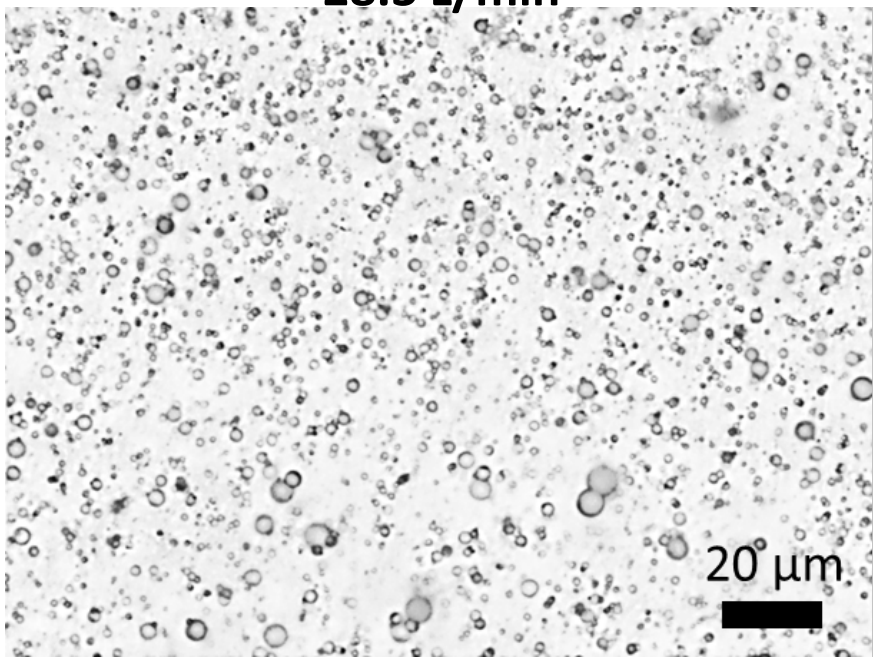


Laser Diffraction Results



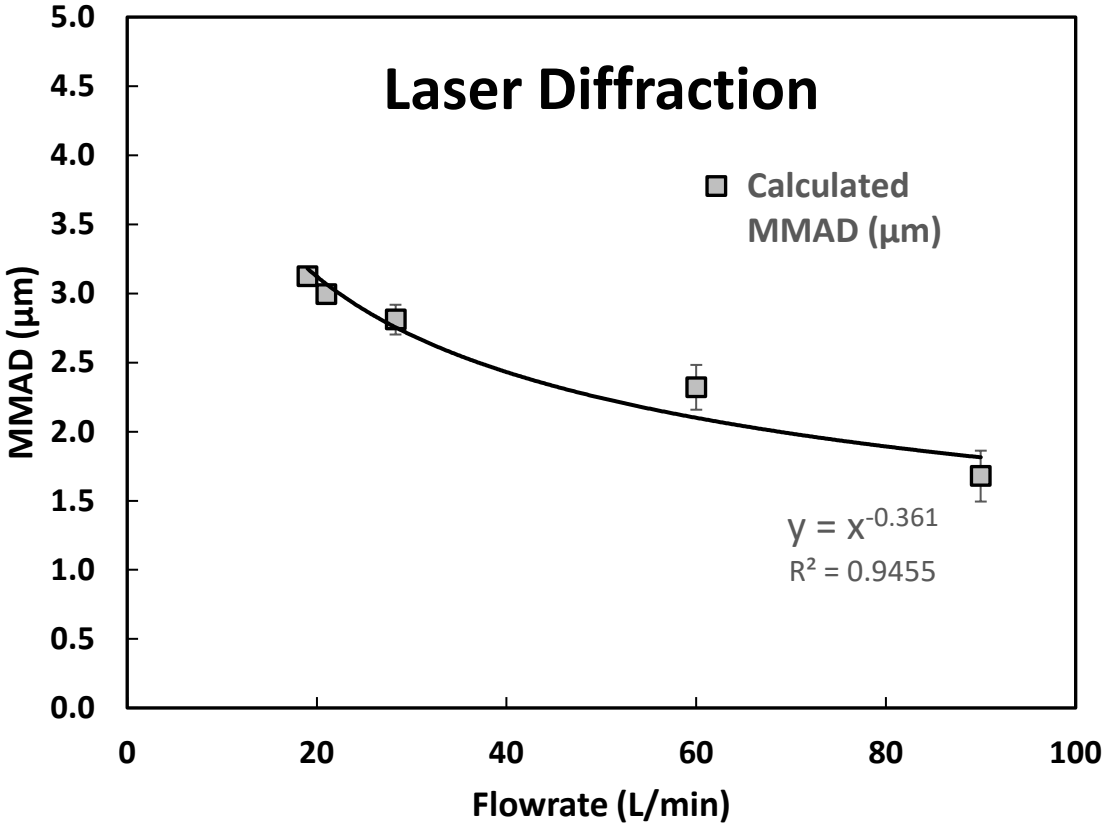
	Dv10	**Dv50**	Dv90
28.3 L/min	1.52	**2.47**	3.74
60 L/min	1.25	**2.04**	3.00
90 L/min	0.79	**1.47**	2.21

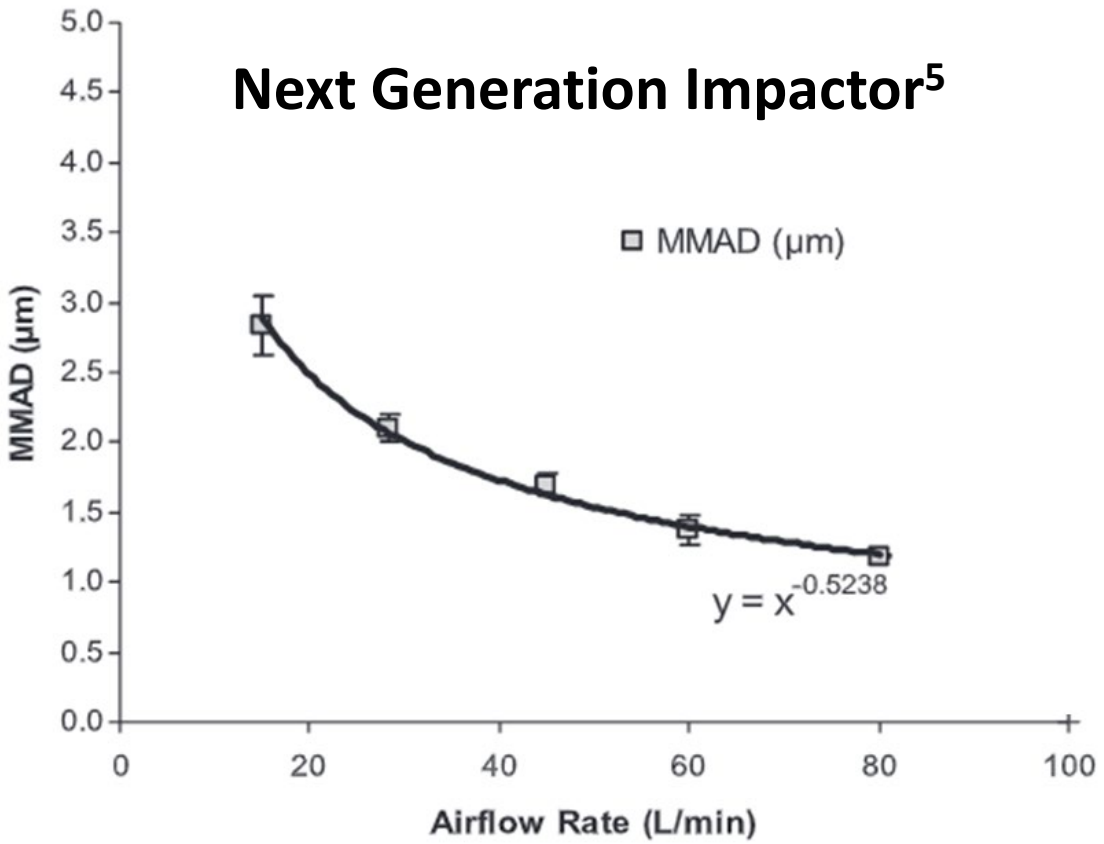
28.3 L/min



- Particle size is flowrate dependent
- Higher flowrates generate smaller particles
- Optical microscopy shows particles are spherical

LD and NGI MMAD Comparison





- LD MMAD showed a similar decreasing trend to NGI MMAD
- Further experimentation and supporting data may be needed to support the suitability of LD to other currently recommended studies characterizing aerosol performance

Product-Specific Guidance (PSG) Development

- **Considerations for Establishment of Bioequivalence (BE):**
  - **Complex** drug-device combination product
  - **Systemic** site of action
  - **Novelty** of delivery device platform
  - Substantial **variability** in loxapine plasma concentrations
  - Outcomes of **internal research**

In Vitro + In Vivo BE Studies

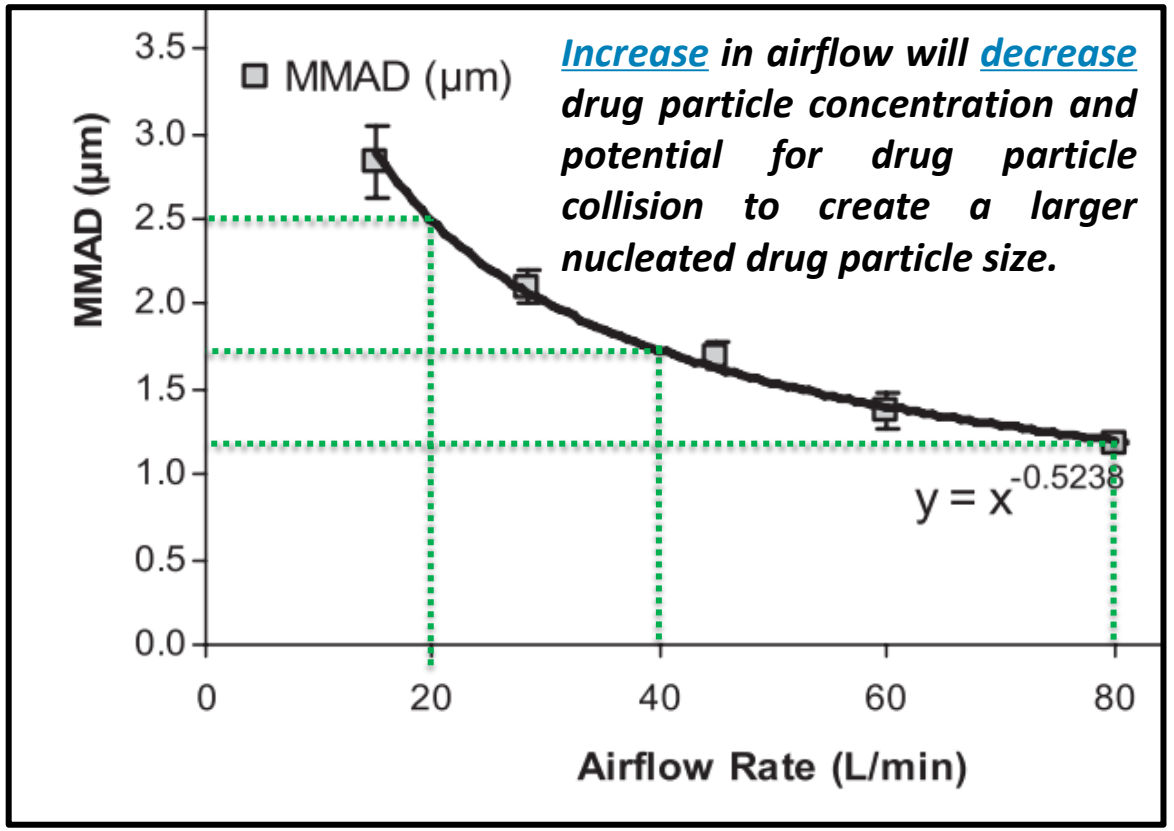
PSG: In Vitro BE Studies

Loxapine Inhalation Powder [4]

Aerodynamic Particle Size Distribution (APSD)

(predict amount of drug deposited within the lungs in different regions based on aerodynamic size)

- Apparatus: Anderson Cascade Impactor, Next Generation Impactor, or another appropriate method
- Flow Rates: **20, 40, 80 L/min**
  - **Supported by OTR's research**
- BE Assessment: PBE analysis of impactor-sized mass (ISM)
- Supportive Evidence: The **cascade impaction (CI) profiles** representing drug deposition on the individual CI stages, mass median aerodynamic diameter (**MMAD**), geometric standard deviation (**GSD**), and fine particle mass (**FPM**)



MMAD vs. airflow rate as measured by NGI.[5]

ISM: the sum of the drug mass on all stages of the CI + terminal filter but excluding the top CI stage because of its lack of a specified upper cutoff size limit

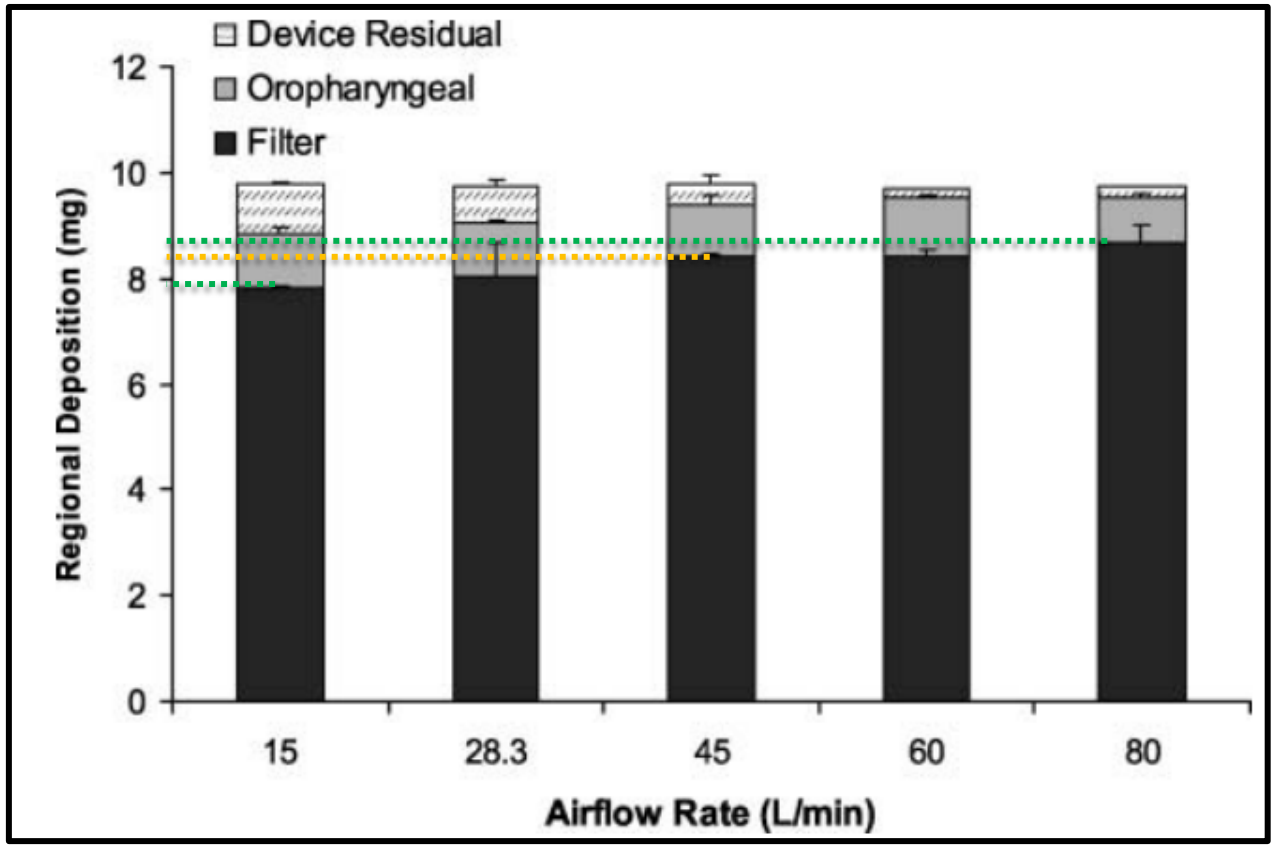
PSG: In Vitro BE Studies cont.

Loxapine Inhalation Powder [4]

Single Actuation Content (SAC)

(Amount of drug exiting device per actuation)

- U.S. Pharmacopoeia (USP) Apparatus B or another appropriate apparatus
- Flow Rates: **20, 40, 80 L/min**
- Equivalence based on: Population bioequivalence (PBE) analysis of SAC



Deposition vs. airflow rate as measured after Alberta idealized mouth-throat model (AIT) unto a filter.[5]

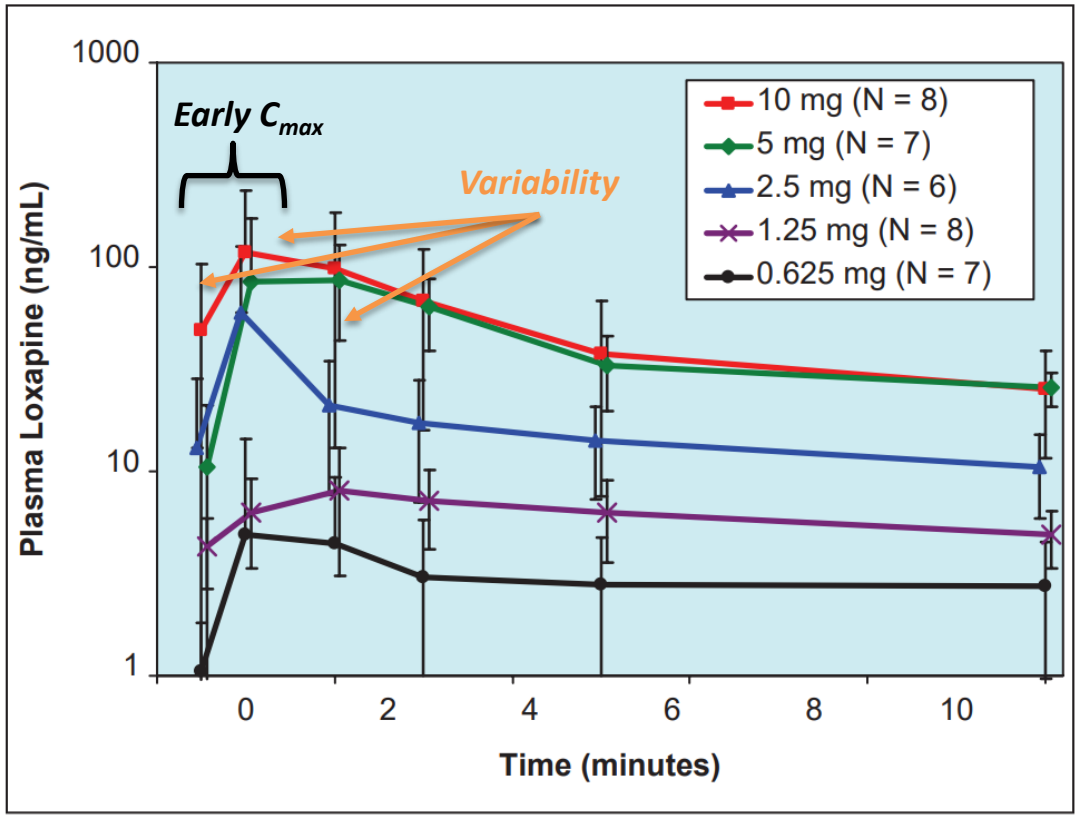
PSG: An In Vivo BE Study

Loxapine Inhalation Powder [4]

Pharmacokinetic (PK) BE Study

(assess systemic bioavailability)

- Design: a fasting, single-dose two-way crossover
- Strength: 10 mg Dose: 10 mg of loxapine (single inhalation)
- Subjects: Healthy males and non-pregnant females
- Additional comments: follow **REMS with an Elements to Assure Safe Use (ETASU)**
- Analyte to measure: Loxapine in plasma
- Equivalence based on: **$AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$**
  - The 90% confidence intervals for the geometric mean T/R ratios of $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$ should fall within the limits of 80.00% - 125.00%
- Supportive Data: C_{max}, T_{max}, partial AUC (10 min, 30 min, 2 hours) to assess onset of loxapine



Plasma concentrations following loxapine administration (mean ± SD); PK population, n = 36.[6]

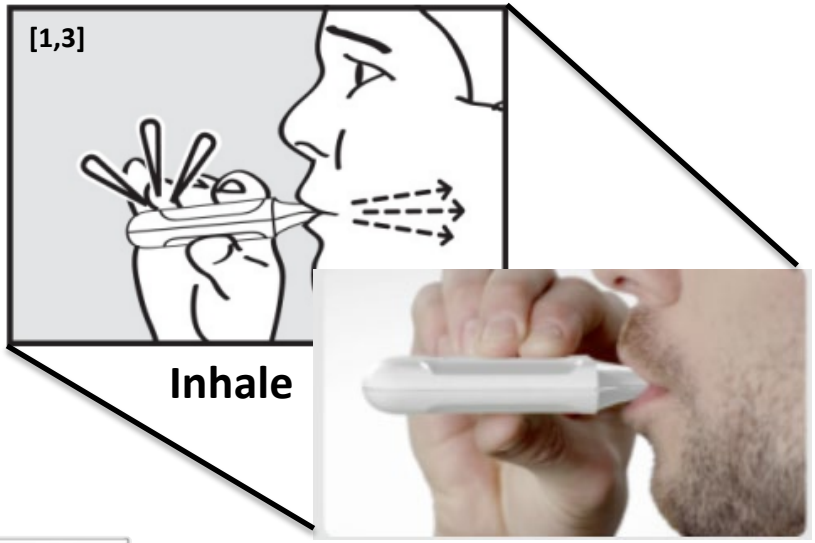
PSG: Additional Information

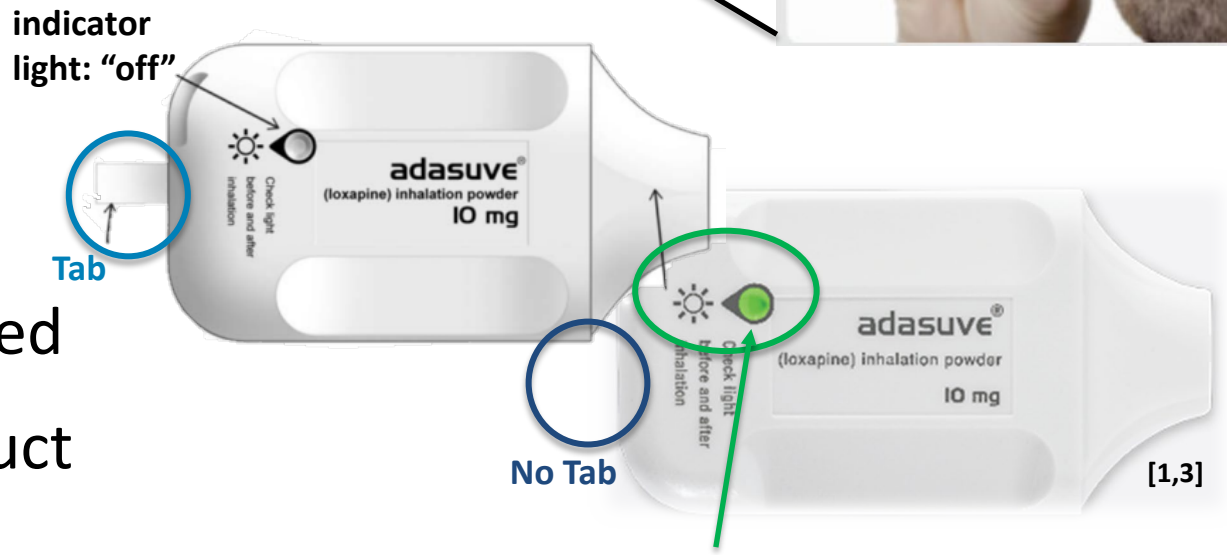
Loxapine Inhalation Powder [4]

Device Considerations

(assessment of the user interface)

- Consider the following characteristics of the RLD product when designing the generic product:
  - **Passive** (breath-actuated), single dose format of the RLD device
  - Device **activation** system
  - **Indicator** that the device is activated
  - Device **resistance** of the RLD product





Summary

- **ADASUVE (Loxapine) Inhalation Powder** is a **single-use drug-device combination product** for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.
- Provides rapid **systemic delivery** of a ***thermally-generated aerosol*** of pure **loxapine** from the Staccato device that is quickly absorbed through the lungs and into the bloodstream**.**
- OTR Research on assessment of ADASUVE:
  - **Further experimentation** and **validation** are required to determine the suitability of ***Laser Diffraction*** as an orthogonal method to other currently recommended studies like ***APSD***.
- Based on OGD's evaluation of the RLD, including OTR's characterization studies and supporting data, the **PSG for *Loxapine Inhalation Powder*** was developed to include the following BE studies:
  - **Single Actuation Content**
  - **APSD**
  - **PK Study**
    - Equivalence: $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$
    - Supportive Data: C_{max}, T_{max}, partial AUC (10 min, 30 min, 2 hours) to assess onset of loxapine

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  - Ethan Stier
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  - Hao Zhu
  - Youwei Bi

References and Resources

1. ADASUVE labeling
2. ADASUVE website
3. ADASUVE Technology
4. PSG on *Loxapine Inhalation Powder*
5. Dinh KV, Myers DJ, Noymer PD, Cassella JV. In vitro aerosol deposition in the oropharyngeal region for Staccato® loxapine. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2010 Aug 1;23(4):253-60.
6. Spyker DA, Munzar P, Cassella JV. Pharmacokinetics of loxapine following inhalation of a thermally generated aerosol in healthy volunteers. *The Journal of Clinical Pharmacology*. 2010 Feb;50(2):169-79.

Challenge Question #1

What are the main bioequivalence (BE) studies included in the product-specific guidance for *Loxapine Inhalation Powder*?

A. Single Actuation Content, Aerodynamic Particle Size Distribution, and Drug Particle Size Distribution by Laser Diffraction

B. Single Actuation Content, Drug Particle Size Distribution by Laser Diffraction, and a pharmacokinetic BE study

C. Single Actuation Content and Aerodynamic Particle Size Distribution, or a pharmacokinetic BE study

D. Single Actuation Content, Aerodynamic Particle Size Distribution, and a pharmacokinetic BE study

Challenge Question #2

What is the effect of inhalation flowrate on ADASUVE inhalation powder particle size?

A. No flow rate dependance

B. Higher flow rates generate smaller particles

C. Higher flow rates generate larger particles

D. 60 L/min inhalations generate the largest particles

Questions?

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