Innovative Technology: Particle Image Velocimetry (PIV) and High Speed Imaging to Support Approval of Generic Orally Inhaled Drug Products

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

Day 2, Session 5: Noteworthy Complex Generic Drug Approvals: Orally Inhaled Products

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Learning Objectives

- Describe the current thinking on regulatory significance of spray velocity for orally inhaled drug products (OIDPs).
- Describe the approach to establish bioequivalence (BE) for inhalation spray drug products.
- Understand and describe the in vitro BE studies recommended in the draft product-specific guidance (PSG) for inhalation spray products, specifically the spray velocity in vitro study.

Spray Velocity Characterization

- Spray velocity characterization provides an additional metric for emitted spray plume characterization.
- There are three main categories of OIDPs that are the focus of Generic Drug User Fee Amendments (GDUFA)-funded research:
  - Metered dose inhalers (MDIs)
  - Dry powder inhalers (DPIs)
  - Inhalation spray inhalers
- GDUFA-funded regulatory science research on spray velocity characterization indicates:
  - Spray velocity measurements have established regulatory significance for inhalation spray products.
  - For certain MDIs and DPIs, there is potential for spray velocity measurements to support regulatory decision-making, but more research is needed.

Inhalation Spray Products

- Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation* (July 2002) defines inhalation sprays as follows:

  *"An inhalation spray drug product consists of the formulation and the container closure system. The formulations are **typically aqueous based** and, by definition, **do not contain any propellant**. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are **intended for delivery to the lungs by oral inhalation for local and/or systemic effects**. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations... The dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects."*

FDA draft guidance for industry, *"Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation" (July 2002)*

Inhalation Spray Products

- To date, there are four inhalation spray drug products approved on the market:

Product name	Active Pharmaceutical Ingredient (API)
COMBIVENT RESPIMAT	albuterol sulfate; ipratropium bromide
STRIVERDI RESPIMAT	olodaterol hydrochloride
SPIRIVA RESPIMAT	tiotropium bromide
STIOLTO RESPIMAT	olodaterol hydrochloride; tiotropium bromide

- According to the approved labeling, these four inhalation spray products utilize the RESPIMAT® Soft Mist™ Inhaler device to produce a ***metered, slow moving aerosol cloud*** following actuation.
- No generic products are available.

https://asthma.org.au/wp-content/uploads/2019/10/Spiriva-Respimat-New-Pack.jpg

Unique Features of Inhalation Sprays

- Inhalation sprays exhibit many similar features to ***aqueous-based solutions for nebulization***, ***aqueous-based solution nasal sprays*** and ***propellant-based solution MDIs***.
- The sprays from inhalation spray products that are currently marketed have the following characteristics:
  - **Aqueous drug solution droplets** (resembling nebulized aerosol)
  - **Longer duration** (e.g., 1.5 seconds; approximately 10 times that of an MDI)
  - **Slow moving aerosol** (velocity approximately 1/10th of that of an MDI)
- These characteristics may impact how the inhalation spray is ***used***, as well as its ***performance***.
- Development of BE recommendations for inhalation spray products has been supported by **GDUFA-funded research**.

Dalby RN et al. International Journal of Pharmaceutics. 2004; 283: 1–9.
Dalby RN. et al. Medical Devices: Evidence and Research. 2011; 4: 145-155.

BE Approach for Inhalation Spray Products

In vitro studies	In vivo studies
➢ Single Actuation Content (SAC) ➢ Aerodynamic Particle Size Distribution (APSD) ➢ Spray Pattern ➢ Plume Geometry ➢ Priming and Repriming ➢ Spray Duration ➢ Spray Velocity	➢ Comparative pharmacokinetic (PK) study with a fasting, single-dose, two-way crossover design in general population ➢ All strengths tested.

Formulation Sameness (Q1 and Q2)* + Device Similarity

*Does **not** recommend a comparative clinical pharmacodynamic (PD) bioequivalence (BE) study*

www.fda.gov Product-specific Guidances for Generic Drug Development

*Q1: Qualitative sameness; Q2: Quantitative sameness

In Vitro BE Study Considerations: Spray Velocity

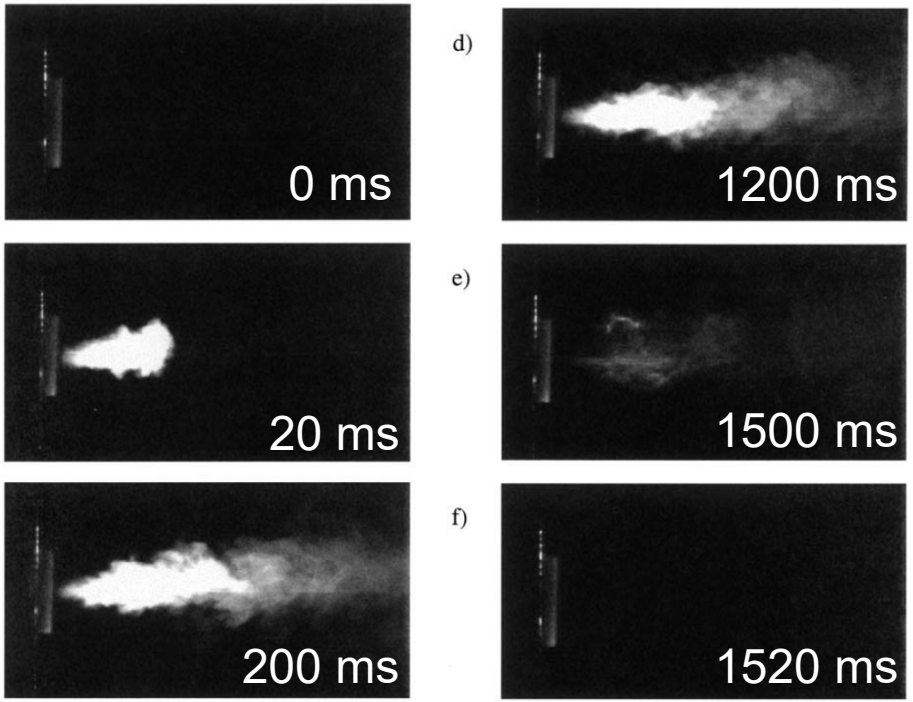
- Design: The spray velocity test should be performed at the B and E lifestages of the product. **High speed imaging, particle image velocimetry, phase Doppler anemometry or other suitable method** may be used to determine spray velocity.
- Equivalence based on: PBE or other appropriate statistical analysis of **plume front velocity* at one selected distance between 8 to 12 cm from the nozzle**. If other statistical analysis is used, it should be adequate considering the purpose of the study and scientifically justified.
- Full plume front velocity vs. distance data should be submitted as supportive evidence for equivalent spray velocity, which may be used to confirm the appropriate distance from the nozzle used for collecting recommended plume front velocity data.

- *The current labeling for marketed inhalation spray products states that the device uses "**mechanical energy to generate a slow moving aerosol cloud of medication**"*
- *Spray velocity is expected to influence drug deposition in the mouth-throat region and in the lungs.*

*Velocity at the front edge of the aerosol cloud.

Spray Velocity: High Speed Camera

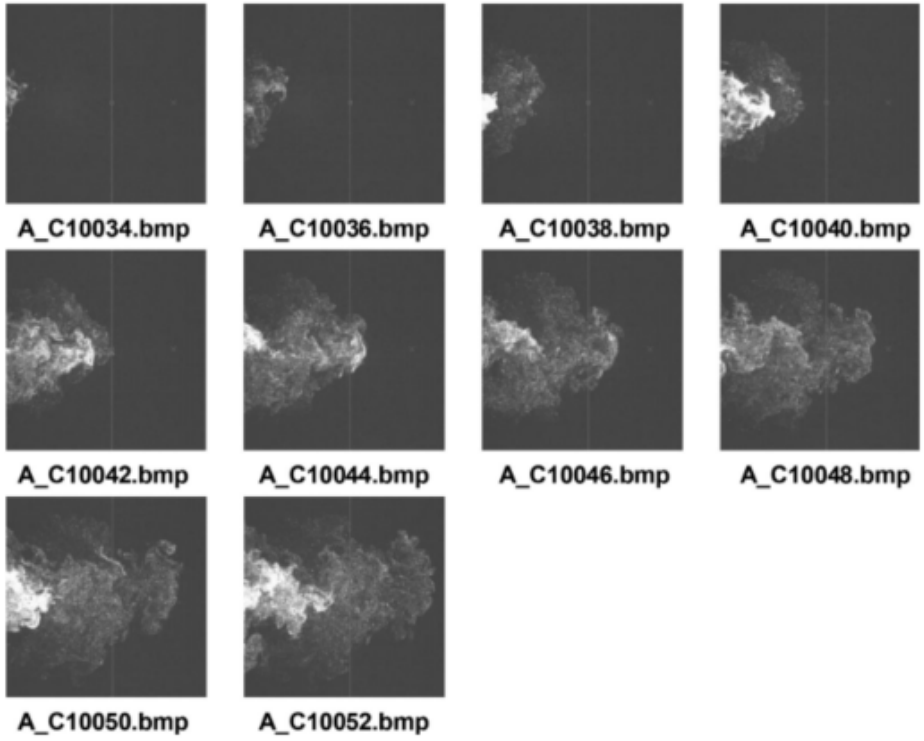
- Hochrainer et al. utilized high-speed video (HSV) recording for determining spray velocity.
- The developing aerosol cloud was photographed using the dark field technique to illuminate the spray.
- Data were collected from the moment the spray begins to develop to the last moment when a spray was formed at the **nozzle outlet.**
- **Plume tip displacement** was measured using a measuring scale.
- **Plume front velocity (PFV)** was determined using a curve fit of the distance versus time data and taking the time derivative of the equation.
- The PFV was determined for the 10 cm distance as measured from the **nozzle outlet** using interpolation.



Hochrainer D et al. Journal of Aerosol Medicine, 2005;18(3):273-82

Spray Velocity: Particle Image Velocimetry

- Tamura et al. utilized particle image velocimetry (PIV) for determining spray velocity.
- The laser light sheet illuminates the spray.
- Data were collected from the moment the spray begins to develop to the last moment when a spray was formed at the **nozzle outlet.**
- The **plume tip displacement** was measured using the image calibration scale.
- PFV was determined using a curve fit of the distance versus time data and calculating the time derivatives at distances of 8 and 10 cm from the **nozzle outlet**.

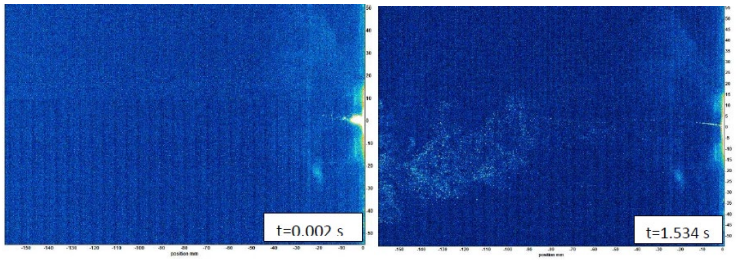


Tamura, G. (2015). *Allergol Int, 64*(4), 390-392; Tamura, G. (2017). Respir Investig. 2017;55(4):287-8. .

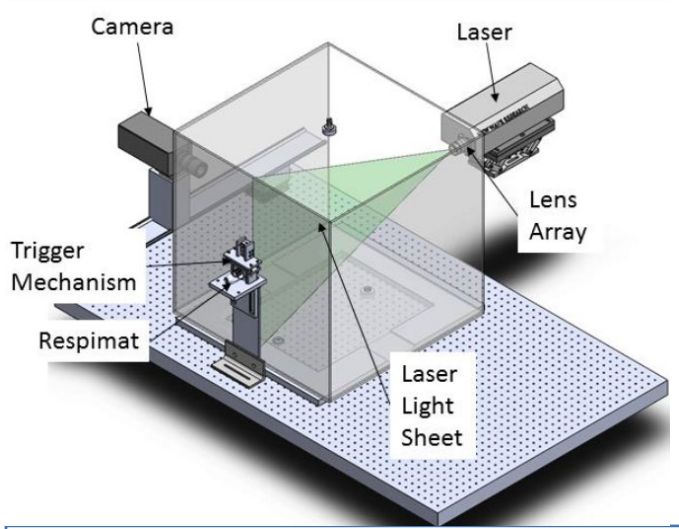
Case Study: Evaluation of spray velocity from tiotropium bromide inhalation spray metered inhalers

PIV Methods

- **PFV** or velocity at the **front edge of the aerosol cloud** was assessed using PIV or HSV recordings of a tiotropium bromide inhaler.
- The PIV image sequence provides images captured from the moment when the spray begins to develop to the last moment when the spray is formed at the nozzle outlet.
- Methods are similar to the approach of Tamura.



Start and End Representative Images.



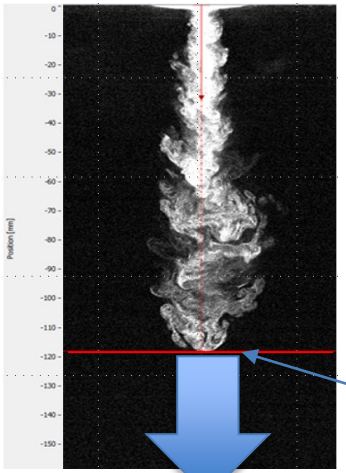
Example experimental set-up for PIV studies: The laser light sheet is in-line with the nozzle of the inhaler and the camera is positioned orthogonally. Synchronization of the PIV system with the inhaler allowed spray resolution.

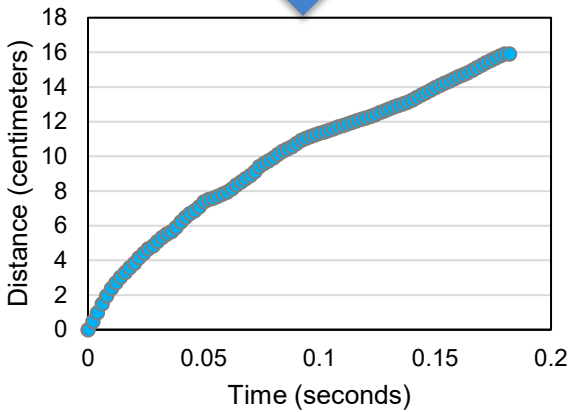
Studies conducted under GDUFA funded research, "Investigating the Impact of Soft Mist Inhaler In Vitro Characteristics on Human Airway Deposition: A Combined In Vitro-In Silico Approach"

Tamura, G. (2015). *Allergol Int, 64*(4), 390-392; Tamura, G. (2017). Respir Investig. 2017;55(4):287-8.

PIV Methods (cont'd)

- The PIV image sequence was used to visually determine the time duration between the beginning of the spray at the nozzle outlet and when the plume tip reaches the edge of the camera frame.
- Software (Spray Geometry®) was used to track the movement of the **front edge of the plume**.
- The elapsed time and the distance traversed by the plume front is collected.

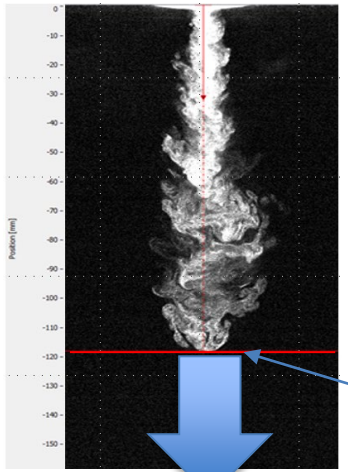




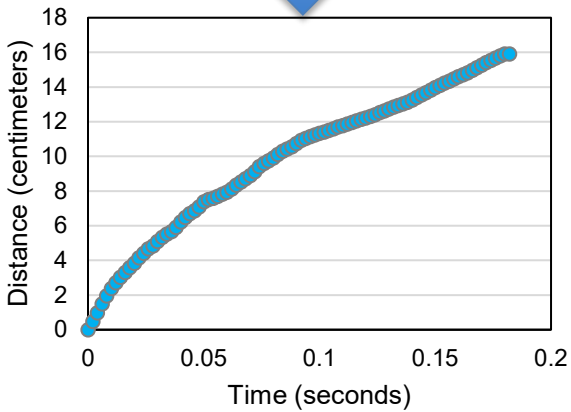
Studies conducted under GDUFA funded research, "Investigating the Impact of Soft Mist Inhaler In Vitro Characteristics on Human Airway Deposition: A Combined In Vitro-In Silico Approach"

PIV Methods (cont'd)

- The velocity is determined by calculating the **slope of the distance versus time curve** using a backward differencing scheme.
- Plume front velocity was determined at 6, 8, 10, 12, and 14 cm downstream of the nozzle outlet.
- To determine the PFV at the specific distance, linear interpolation was used.



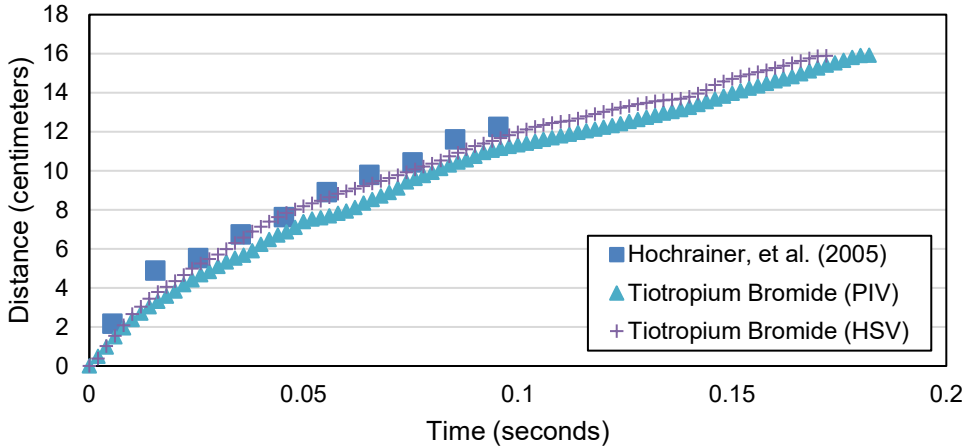
Software tracks the plume front

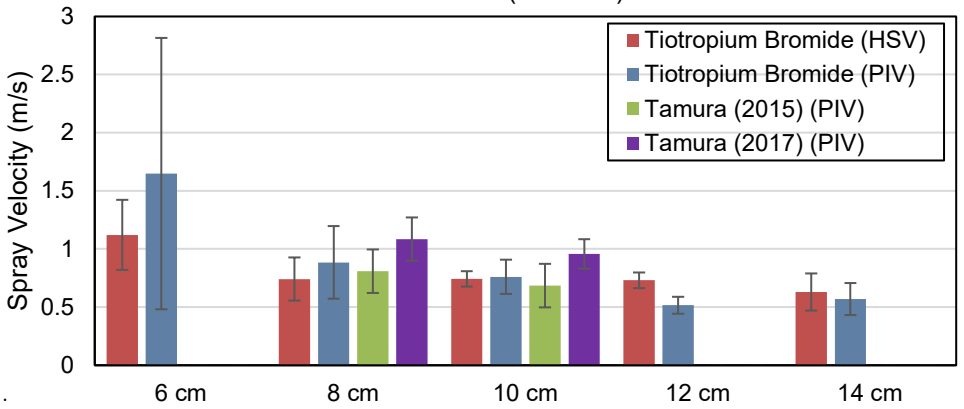


Studies conducted under GDUFA funded research, "Investigating the Impact of Soft Mist Inhaler In Vitr Characteristics on Human Airway Deposition: A Combined In Vitro-In Silico Approach"

PIV Results

- Tiotropium bromide distance vs. time curves were assessed with HSV and PIV and compared with literature data.
- The distance versus time curve is consistent with the work of Hochrainer, et al. for an inhalation spray using the Respimat inhaler.
- PFV measurements were consistent with findings by Tamura.
- A comparison cannot be made for PFV data in Hochrainer, et al. because a tiotropium bromide inhalation spray was not tested.



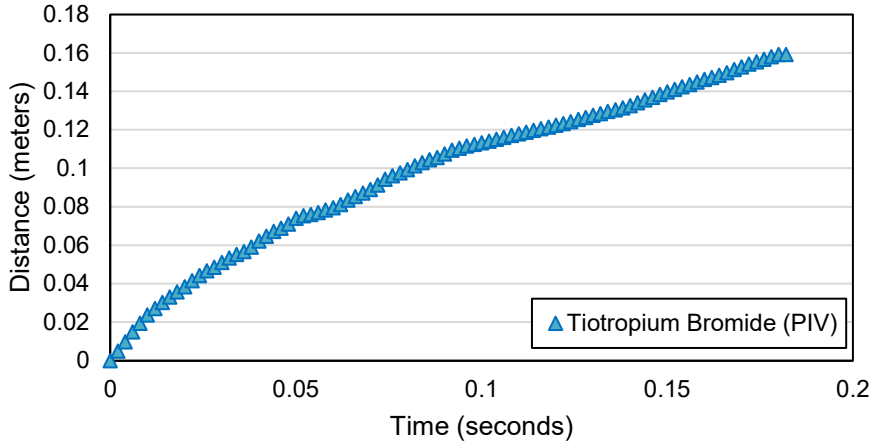


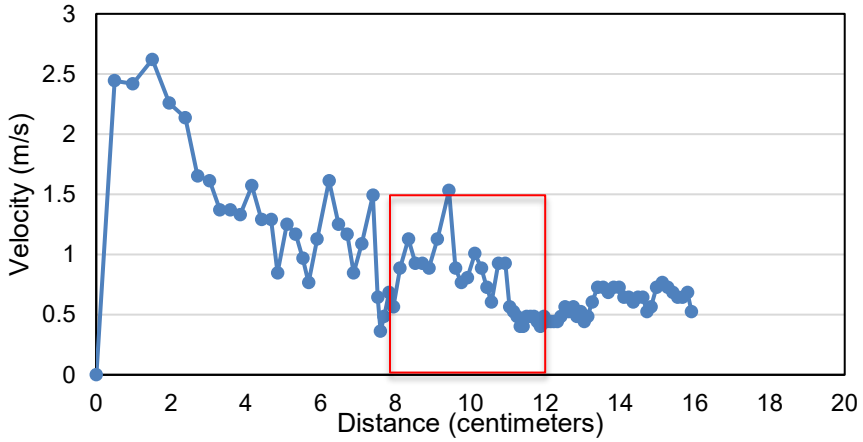
Hochrainer D et al. Journal of Aerosol Medicine, 2005;18(3):273-82

Tamura, G. (2015). *Allergol Int, 64*(4), 390-392; Tamura, G. (2017). Respir Investig. 2017;55(4):287-8. .

PIV Results

- The selected distances of 6, 8, 10, 12, and 14 cm were assessed on the velocity vs. distance curve to find the most appropriate distances for assessment of spray velocity.
- An **8-12 cm distance range** was selected due to relatively low variability in the region beyond 6 cm and comparison to literature data.
- In addition to PFV data at the selected distance used for PBE analysis, the draft PSG on ***Tiotropium Bromide Inhalation Spray*** (Recommended Nov 2020), also recommends prospective applicants consider submitting full PFV versus distance data as additional supportive information.





In Vitro BE Study Design Considerations: Other Methods

- Any suitable method may be used, provided the methods are appropriate for assessing spray velocity, and adequately sensitive in detecting velocity differences between test (T) and reference listed drug (RLD) inhalation sprays.

It is encouraged that prospective applicants submit a pre-ANDA Product Development Meeting request to discuss their method development and statistical analysis plan for spray velocity study designs

- Refer to FDA guidance for *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2017).
- Meeting package should include details on the method development, validation, preliminary results (if any), and proposed statistical analysis plan.

Conclusions

- Inhalation sprays are propellant-free, typically ***aqueous-based*** formulations containing drug products intended for ***delivery to the lungs by oral inhalation*** for local and/or systemic effects.
- Establishment of BE for inhalation sprays is based on the ***weight-of-evidence approach*** consisting of in vitro and in vivo studies.
  - For ***spray velocity*** studies, the ***plume front velocity*** at one selected distance between 8 to 12 cm from the nozzle should be measured using a suitable and sensitive technique.
  - Full plume front velocity vs. distance data also serve as additional supportive information.
- **Prospective applicants are encouraged to submit a pre-ANDA Product Development Meeting for discussing with the Agency their development program for inhalation spray products.**

Future Work

- FDA is currently working on completing the RLD arm of the spray velocity study for tiotropium bromide inhalation metered spray.
- The data from this study will be published when available.

Challenge Question #1

Plume front velocity is velocity defined at what specific location?

A. Velocity at the front edge of the aerosol cloud.

B. Average velocity along the centerline of the fully developed plume profile.

C. Maximum velocity measured a central location downstream from the inhaler nozzle.

D. Average velocity measured only at the inhaler nozzle.

Challenge Question #2

Plume front velocity may be determined from which of the following data sets:

A. PIV data

B. High speed imaging data

C. Both A and B

D. Neither A or B

Call to Action

If you have questions regarding a spray velocity study, consider requesting a pre-ANDA product development meeting.

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Resources

- FDA draft guidance for industry, *"Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation" (July 2002)*
- Draft PSG for *Tiotropium bromide inhalation spray metered* (Recommended Nov 2020, RLD: SPIRIVA RESPIMAT)
- 21 CFR §320.23 Basis for measuring in vivo bioavailability (BA) or demonstrating bioequivalence (BE).
- FDA draft guidance for industry, *"Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (January 2017)* FDA draft guidance for industry, *Controlled Correspondence Related to Generic Drug Development* (December 2020)
- FDA final guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (November 2020)
- https://www.respimat.com/disposable/
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