Demonstrating Bioequivalence with Inhalation Spray Drug Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 2: Nasal and Inhalation Products

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Learning Objectives

- Describe the approach to establish bioequivalence (BE) for inhalation spray products.
- Understand and describe the in vitro BE studies recommended in the draft product-specific guidances (PSGs), specifically:
  - Aerodynamic Particle Size Distribution (APSD)
  - Spray Duration
  - Spray Velocity
- Describe the current thinking on device sameness of inhalation spray products.

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FDA draft guidance for industry, *"Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation" (July 2002)*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

- Currently, 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 their approved labeling, these four inhalation spray products utilize the RESPIMAT® Soft Mist™ Inhaler device to produce a ***metered, slow moving aerosol cloud*** following actuation.

Challenges in Establishing BE

- Inhalation sprays exhibit many similar features to ***aqueous-based solutions for nebulization***, ***aqueous-based solution nasal sprays*** and ***propellant-based solution MDIs***.
- The spray 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** (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 **Generic Drug User Fee Amendments (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

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tiotropium Bromide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Tiotropium bromide
Dosage Form; Route:	Spray, metered; inhalation
Strengths:	EQ 0.0025 mg Base/inh EQ 0.00125 mg Base/inh
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) inhalation sprays containing tiotropium bromide.

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Recommended Nov 2020

BE Approach for Inhalation Spray Products

Formulation Sameness (Q1 and Q2)* + Device Similarity

*Does **not** recommend a comparative clinical pharmacodynamic BE study*

*Q1: Qualitative sameness; Q2: Quantitative sameness

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*Q1: Qualitative sameness; Q2: Quantitative sameness

In Vitro BE Study Considerations: APSD

- Spray properties from an inhalation spray product resemble that of a nebulized aerosol containing aqueous droplets.
- To improve the robustness and repeatability of the measurements, it is recommended that water evaporation be minimized by:
  - Performing the APSD test under **high humidity** conditions (as close as possible to 100% relative humidity), or
  - By cooling the cascade impactor (CI) to **low temperatures** (e.g., 5°C) or by any other suitable method.

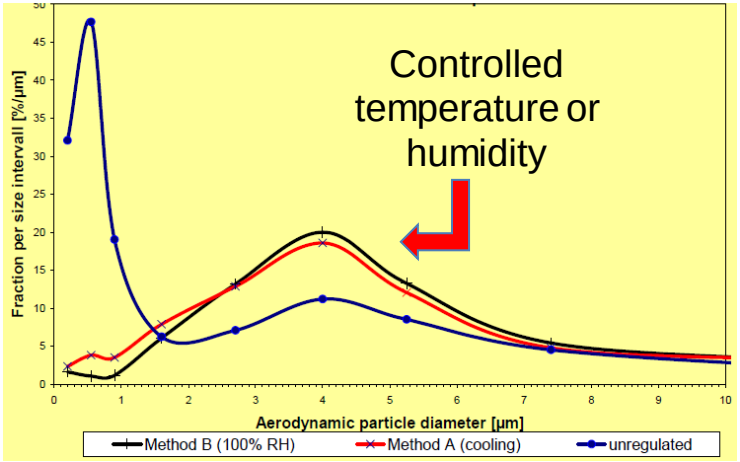
In Vitro BE Study Considerations: APSD

Method A (cooling)

Impactor 28.3 L/min, ≤5°C. Room condition: 22 ± 1°C and RH = 45 ± 5%

Method B (100% RH)

Impactor 28.3 L/min equilibrated at 100% RH



Method A (cooling)	Method B (100 % RH)
• Ease of use • Humidifier not necessary (less expensive)	• Prevent slight evaporation as occurred with method A (cooling) • Controlled constant conditions during time of measurement (even at measuring times > 5 minutes) • Independent of prevalent room conditions • Higher throughput due to less equilibration times (30 vs. 90 minutes) • Suitable for automation

Hubrath T and Kumb J. Drug Delivery to the Lungs 2008. Edinburgh, UK.

In Vitro BE Study Considerations: Spray Duration

- Design: The spray duration test should be performed at the beginning and end lifestages of the product. **Video recording with a high-speed camera, laser light diffraction, particle image velocimetry** or other suitable method may be used to determine the spray duration.
- Equivalence based on: Population BE (PBE) analysis of the **time interval when the spray begins to develop, to the last moment when a spray is formed at the nozzle.**

- *The current labeling for marketed inhalation spray products states that: "**duration of inspiration should be at least as long as the spray duration (1.5 seconds)**."*
- *Since inhalation sprays can have longer spray durations, the coordination between the actuation of the product and the patient breathing may be affected by differences in spray duration.*

In Vitro BE Study Considerations: Spray Velocity

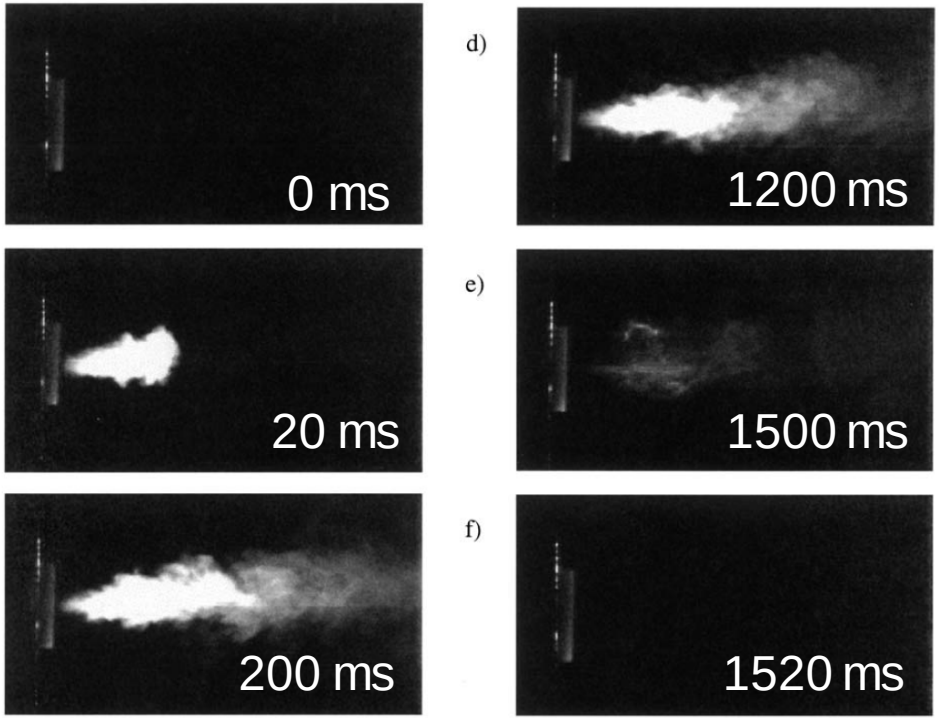
- Design: The spray velocity test should be performed at the beginning and end lifestages of the product. **High speed imaging, particle image velocimetry, phase doppler anemometry, or other suitable method** may be used to determine spray velocity.
- Equivalence based on: PBE or other appropriate statistical 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.

- *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.

Study Design Considerations: High Speed Camera

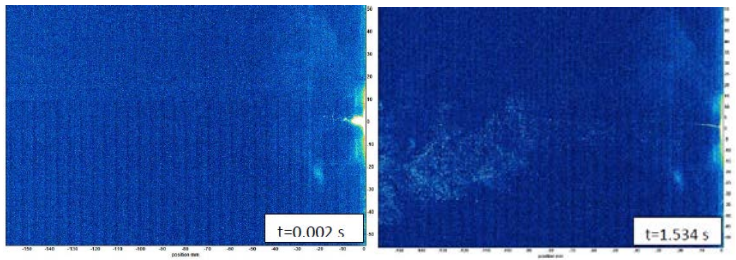
- Hochrainer et al. utilized video recording for determining spray duration and velocity.
- For spray duration, **number of video frames** were counted from the moment the spray begins to develop to the last moment when a spray was formed at the **nozzle outlet** at a speed of over 100 frames per second.
- The **plume front velocity** was measured by photographing the developing aerosol cloud using dark field technique to illuminate the spray.



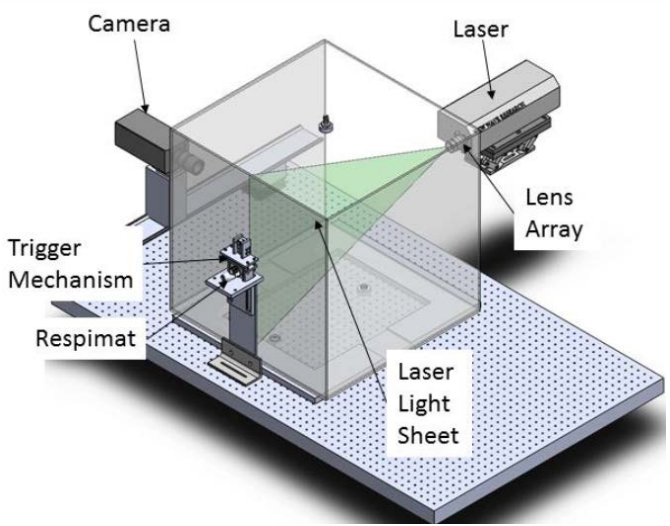
Hochrainer D et al. Journal of Aerosol Medicine, 2005;18(3):273-82

Study Design Considerations: Particle Image Velocimetry

- In an internal research study, particle image velocimetry (PIV) image sequence was used to visually determine the duration between the beginning of the spray and the end of the spray from the nozzle.
- Number of frames were counted (time resolution was 0.002 seconds per frame) for spray duration.



Beginning and End Representative Images

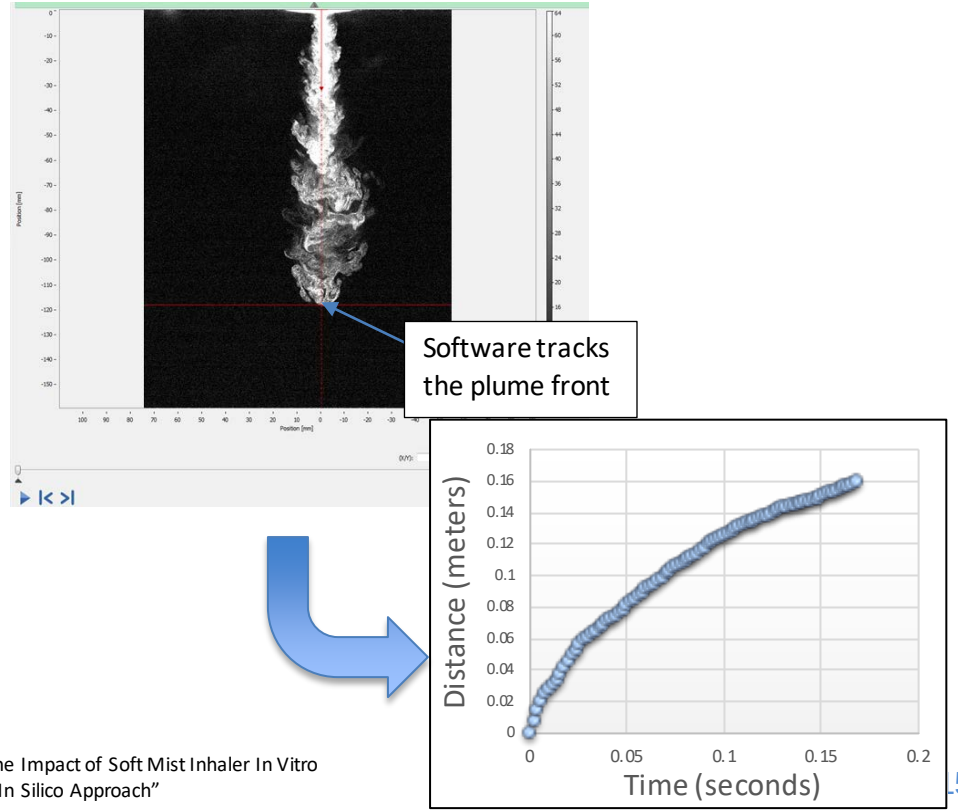


Example experimental set-up for PIV studies: The laser light sheet is in-line with the nozzle of the inhaler and the camera is positioned orthogonally. Synchronization of the PIV system with the inhaler allowed spray resolution.

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"

Study Design Considerations: Particle Image Velocimetry

- A similar PIV set-up as the spray duration was used in combination with software to track the movement of the **front edge of the plume**.
- To determine the plume front velocity at the specific distance (**between 8 to 12 cm from the nozzle**) linear interpolation was used.



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"

Study Design Considerations: Other Methods

- Any suitable method may be used, provided the methods are appropriate for assessing spray duration or spray velocity, and adequately sensitive in detecting spray duration and velocity differences between test and reference 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 duration and 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.

Device Considerations for Inhalation Spray Products

- The draft PSG on *Tiotropium Bromide Inhalation Spray* (Recommended Nov 2020), recommends prospective applicants consider the following characteristics of the reference product when designing the test product:
  - **Active, metered, multi-dose device**
  - **Size and shape of the reference product**
  - **Number of doses in the reference product**
  - **External operating principles and external critical design attributes of the reference product**
  - **Dose indicator/counter**
- Communications regarding the device interface and device evaluation:
  - **Controlled correspondences (Response within 60 days of submission date)**
  - **Pre-ANDA product development meeting requests (Response within 120 days of the grant letter)**
- Information needed for a Device Evaluation
  - **Samples of test and reference listed drug (RLD) devices**
  - **Complete comparative (threshold) analyses**
  - **Specific question(s) related to the comparative (threshold) analyses**

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)

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 ***APSD*** studies, it is recommended that water evaporation be minimized by testing under ***high humidity*** conditions or by ***cooling*** the cascade impactor or by any other suitable method.
  - For ***spray duration*** studies, the time interval when the spray begins to develop, to the last moment when a spray is formed at the nozzle should be measured using a suitable and sensitive technique.
  - 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.
- Key device characteristics including external operating principles, external critical design attributes and presence of dose counter should be considered when developing the test inhalation spray product.
- **Prospective applicants are encouraged to submit a pre-ANDA Product Development Meeting for discussing with the Agency their development program for inhalation spray products.**

Challenge Question #1

Spray duration of an inhalation spray can be measured using which of the below techniques?

A. High speed camera

B. Particle image velocimetry

C. Laser diffraction

D. All of the above

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  - Changning Guo, PhD
  - Jason Rodriguez, PhD
- FDA/CDER/OGD/OSCE
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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/
- Hochrainer D, Hölz H, Kreher C, Scaffidi L, Spallek M, Wachtel H. Comparison of the aerosol velocity and spray duration of RESPIMAT Soft Mist Inhaler and pressurized metered dose inhalers. *J Aerosol Med.* 2005; 18(3): 273-282.
- Hubrath T and Kumb J. Drug Delivery to the Lungs 2008. Edinburgh, UK
- Tamura G. Comparison of the aerosol velocity of RESPIMAT soft mist inhaler and seven pressurized metered dose inhalers. *Allergol Int.* 2015; 64: 390-392.
- Dalby RN et al. International Journal of Pharmaceutics. 2004; 283: 1–9.
- Dalby RN, Eicher J, Zierenberg B. Development of RESPIMAT Soft Mist Inhaler and its clinical utility in respiratory disorders. Medical Devices: Evidence and Research. 2011; 4: 145-155.
- Saluja B, Li BV, Lee SL. Bioequivalence for Orally Inhaled and Nasal Drug Products. In: Yu LX, Li BV, editors. FDA Bioequivalence Standards. New York: Springer; 2014. p. 369-394.

Questions?

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https://www.fda.gov/drugs/generic-drugs/science-research