

Quantitative Studies to Inform PSG Development for Tiotropium Bromide Inhalation Spray, Metered

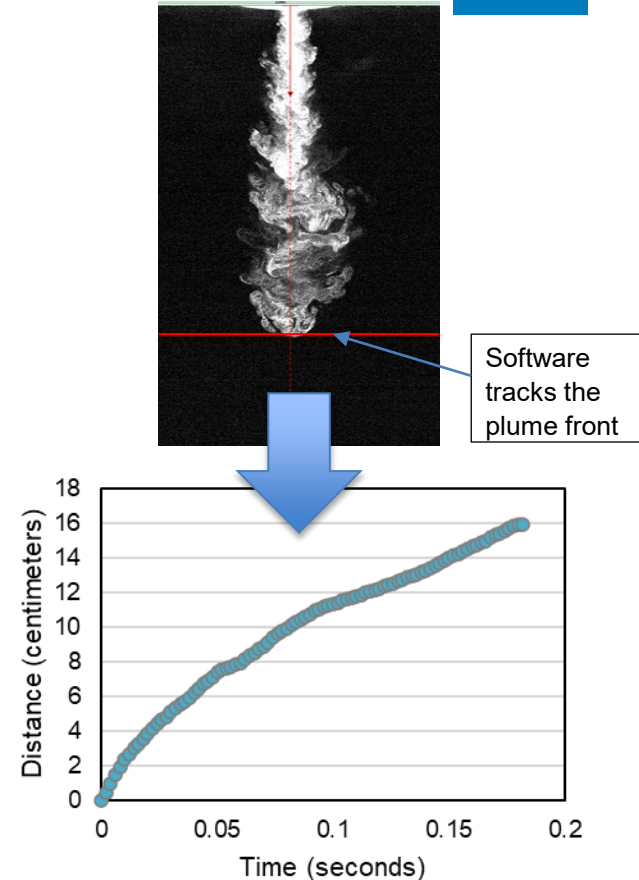
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Objective: Particle image velocimetry (PIV) and high-speed videography (HSV) data were collected to assist in drafting the recommendations for in vitro bioequivalence spray velocity study, which is considered an important metric due to the slow-moving nature of the aerosol cloud from the device.

Spray Velocity Studies

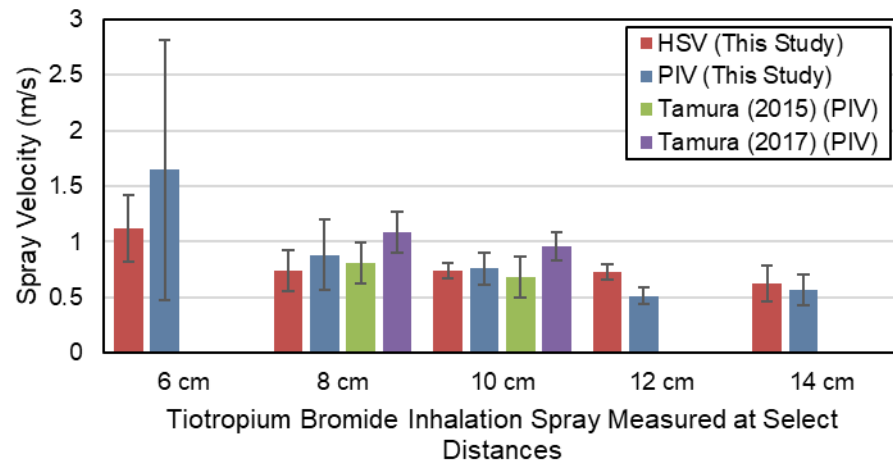
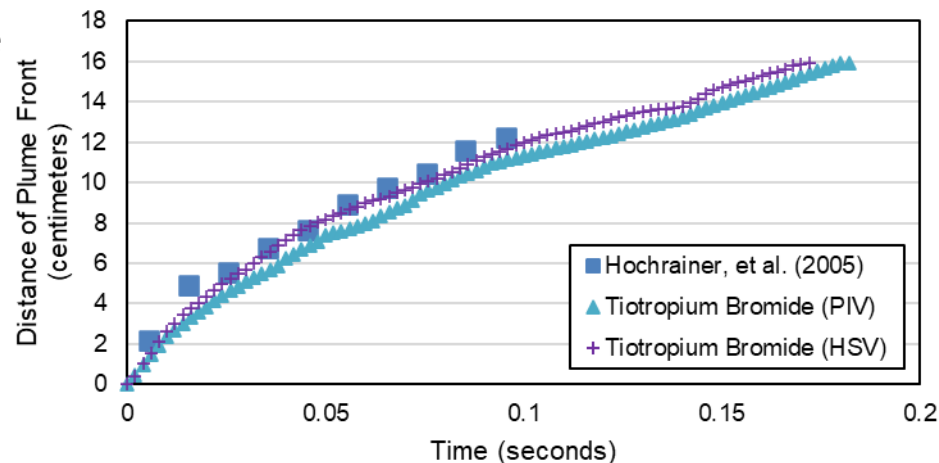
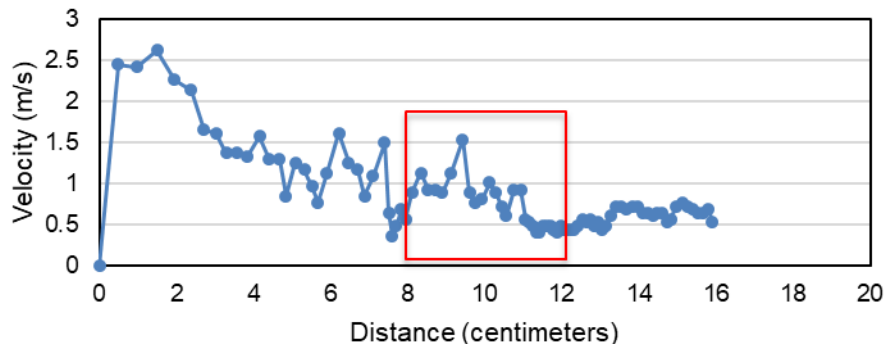
- **Plume front velocity** or velocity at the **front edge of the aerosol cloud** was assessed using **PIV or HSV** recordings of the tiotropium bromide inhalation spray, metered.
- Software (Spray Geometry®) was used to track the movement of the **front edge of the plume**.
- The elapsed time and the distance traversed by the plume front were collected.
- The velocity was determined by calculating the **slope of the distance versus time curve**.
- Plume front velocity was determined at 6-, 8-, 10-, 12-, and 14 cm downstream of the nozzle.
- To determine the plume front velocity at the specific distance, linear interpolation was used.



Results



- Tiotropium bromide distance vs. time curves were assessed with both PIV and HSV and compared to an ipratropium bromide/fenoterol formulation distance vs. time curve from the literature.
- The selected distances were assessed on the velocity vs. distance curve to find the most appropriate distances for assessment of spray velocity; plume front velocity data
- An **8-12 cm distance range** was selected (less variable measurement) and based on comparison to plume front velocity literature data.



Conclusions and Regulatory Impact



- Conclusions:
 - Plume front velocity is best measured 8-12 cm from the nozzle due to relatively low variability in the region beyond 6 cm from the mouthpiece. Full plume front velocity vs. distance data also serve as additional supportive information.
- Regulatory Impact:
 - An in vitro bioequivalence spray velocity study is recommended in the product-specific guidance on ***Tiotropium Bromide Inhalation Spray, Metered*** for comparative evaluation of plume front velocity of the spray plume for a proposed generic product with the reference standard.
 - 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: Population bioequivalence analysis of **plume front velocity at one selected distance between 8 to 12 cm** from the nozzle.