DOE Analysis of Effects of Spacer Handling on In Vitro MDI Performance Characteristics I: Flow Rate and Inhalation Delay
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Purpose
Spacer devices, or valved holding chambers (VHCs), often used in young children to coordinate MDI actuation with inhalation, collect the larger particles that would otherwise be deposited in the oropharynx, emitting only the finer particles into the lung. This poster discusses in vitro testing done to evaluate multiple factors that may alter the respirable dose. A Design of Experiments (DOE) analysis is made on the effects of variable delay between MDI actuation and introduction of the aerosol into an Andersen Cascade Impactor (ACI) for VHCs used at an estimated pediatric inspiratory flow rate. Multiple response factors (performance characteristics) are assessed.

Methods
ACI measurements were conducted for three MDI products and two VHCs using a specially-designed system that can operate the ACI at 28.3 lpm whether employing pediatric inspiratory flow rates (11 lpm) or the standard adult rate, and with variable delay times (0 and 5 sec) between MDI actuation and introduction of the aerosol into the ACI. Determination of deposited doses and aerodynamic particle size distribution used validated HPLC methods. A 2-level, 3-factor full-factorial DOE design was applied to assess the influences of spacer type, flow rate and inhalation delay on seven performance characteristics for each MDI product.

Results
The DOE study shows the presence and type of spacer have the major effect on emitted dose and respirable fraction. In addition to the spacer effect, the inhalation delay has the most significant influence on most MDI performance metrics - emitted dose, respirable dose and fraction (aerosols between 1.1-4.7 µm), and fine particle dose and fraction (FPD and FPF, aerosols under 4.7 µm). MMAD has a more complicated response pattern, with spacer type, inhalation delay time and some interaction factors related to delay time all showing effects.

Conclusion
This study illustrates the use of DOE analysis to effectively assess the effects of spacer handling parameters (flow rate and inhalation delay) on the performance of MDI drugs. The Agency may use these results to determine the data necessary to inform safe and effective use of MDI products when used in conjunction with spacer devices in children.