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Title: Breaking microgram barrier to conduct dose ranging studies with long acting bronchodilators from a novel cosuspension metered dose inhaler product platform

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Body: Dose and exposure response analyses of glycopyrrolate (GP; Reisner C, et al. Eur Respir J 2010; 36: Suppl. 54, 829s) and formoterol fumarate (FF; Orevillo C, et al. Eur Respir J 2010; 36: Suppl. 54, 829s) predict the need to manufacture submicrogram strengths of these drugs for proper assessment of their safety and efficacy profile, including identification of sub-therapeutic doses. We report use of engineered particles to form dose proportional and stable metered dose inhalers (MDI) over a wide dose range for each drug with nanogram level precision. Methods: GP MDIs from 300 ng to 18 µg/actuation, and FF from 480 ng to 9.6 µg, were prepared by cosuspending micronized crystals of each drug in HFA with spray-dried distearoyl-phosphatidylcholine (DSPC) porous particles. Aerodynamic particle size distribution (aPSD) and delivered dose uniformity (DDU) were assessed at a flow rate of 30 L/min. Robustness was assessed by thermal cycling (-5.0°C to 40°C every six hours for 4 weeks), and isothermal storage at room and elevated temperatures. Results: The in vitro drug delivery and aPSD for GP, in mono and combination MDIs with FF, were found to be linearly dose proportional ($r^2 > 0.99$) over the entire dose range, with stable aPSD and DDU under each storage condition. Similar performance was observed for FF MDIs. Conclusions: Pearl's cosuspension platform is capable of generating dose proportional and stable MDIs even with submicrogram doses. Clinical studies are now feasible with an unprecedented dose range of such drugs for a complete benefit-risk assessment.