ABSTRACT:

Measurements for OINDP Quality – I: Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD)

Dr. Jolyon P. Mitchell Ph.D., FRSC (UK), C.Chem., C.Sci.

There are two principal metrics associated with OINDP quality assessments: (1) **delivered dose uniformity** (DDU), in which the total mass of active pharmaceutical ingredient(s) in the airborne particulate from the inhaler is quantified using the **Dose Uniformity Sampling Apparatus** (DUSA), and (2) **aerosol aerodynamic particle size distribution** (APSD) that is determined by **multi-stage cascade impactor** (CI). Both DDU and APSD are critical quality attributes for determining inhaler performance and their determination is described in the pharmacopeial compendia. DDU addresses the quantification of the stability of dose delivery across several inhalers of the same lot, examining performance at beginning and end of the life of the inhaler. As with all types of dosage form, DDU is important as the means to assure reproducible dose delivery. APSD determination is important because likely deposition of inhaled medication in the various regions of the human respiratory tract is highly size dependent.

The presentation begins by focusing on DDU determination, examining the DUSA configurations appropriate for the various inhaler types, and then looking at specification setting and data assessment using parametric tolerance interval testing. The second and larger part of the presentation examines the various CI systems in use for APSD assessments. The multi-stage CI or liquid impinger are the standard apparatuses in the pharmacopeial compendia for the aerodynamic particle size analysis of aerosols from orally inhaled products. A modification of this technique with reduced number of collection stages may also be useful to quantify the mass of particles larger than about 10 µm aerodynamic diameter that might undesirably penetrate beyond the nasopharynx and enter the lungs, associated with nasal drug delivery products. The full resolution CI method is described, looking at the underlying operating principle of inertial size fractionation in the Stokesian regime. The limitation of the CI as a predictive tool for particle deposition location in the respiratory tract and the consequence this restriction places on the interpretation of data are also reviewed. Next, the most frequently encountered CI types are presented before going on to examine the roles of the induction port inlet and pre-separator (if needed). The many factors responsible for introducing measurement variability (precision) are discussed, as are ways to avoid measurement bias (inaccuracy). The presentation continues with an examination of some oral inhaler-specific issues. The presentation concludes by examining how CI-based methods are being used in the context of evaluating nasal drug delivery products for fine droplets that might penetrate beyond the nasopharynx into the lungs, and thereby affect the safety profile of the drug product.

August 2018