ABSTRACT:

Measurements: Particle Size Measurements for OINDP Quality – 2: Alternatives to the Cascade Impactor

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The multi-stage cascade impactor or liquid impinger are the most widely used methods for the quantification of orally inhaled drug delivery products because they determine quantitatively drug mass apportioned to particle aerodynamic size, seen as predictive of likely deposition in the human respiratory tract. However, these methods, even when abbreviated, are time-consuming and require a high degree of operator knowledge and skill concerning how to mitigate sources of measurement bias and intrinsic variability. Especially in early phase product development, it is therefore highly desirable to seek alternative techniques requiring less in the way of know-how to set up and use. After introducing the differences between aerodynamic and non-aerodynamic particle size distribution methods, attention is focused on the technique of laser diffractometry (LD). Although determining non-aerodynamic diameter-based particle size, LD has become an accepted standard method for assessing droplet size distributions from nebulizing systems, because the distinction between the two size descriptors is unnecessary when sampling aqueous droplets. The underlying theory is explored to help identify both strengths and limitations of this technique. LD has also been used with some success in the performance evaluation of the other inhaler types, but care is needed in the interpretation of the resulting data, especially for non-spherical particles. Traceability to active pharmaceutical substance is mostly unavailable with optical methods such as LD, but LD can be made non-invasive (no sampling needed) and is rapid to execute. LD is therefore becoming increasingly important in the context of Process Analytical Technology (PAT) and Quality by Design (QbD) initiatives that are being encouraged by regulatory agencies in product submissions. Laser (phase) Doppler particle analysis (PDPA) is an alternative approach, as it can also yield valuable information about the flow field surrounding the aerosol particles whilst in transit from the inhaler to the patient. However, this technique requires a high degree of skill to operate successfully and only a small portion of the aerosol is sampled. Time-of-Flight (TOF) methods have been used for the past 20 years with a limited degree of success, as they, like the cascade impactor, provide aerodynamic particle size directly. However, TOF-based methods are subject to a number of sources of potential bias and most importantly, drug mass is not apportioned directly to particle size. The presentation concludes with a look at automated microscopy combined with image analysis, making it feasible to survey many tens of thousands of particles in terms of their physical size in a short time period. Although drug mass is not apportioned to size in conventional microscopy, the incorporation of Raman Chemical Imaging (RCI) now makes this process possible. Microscopy-RCI is therefore becoming a key tool in the product development phase.

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