Introduction

Many methods have been applied to the description of the Aerodynamic Particle Size Distribution (APSD) of Orally Inhaled Products (OIP) with varying degrees of success. Currently the most common, regulatory acceptable means of doing so is sums of stages of either an Anderson Cascade Impactor (ACI) or Next Generation Impactor (NGI).

The ability of sums of stages to detect shifts in the APSD has recently been questioned by JFAC-RS and the alternative of the simple ratio of large particle mass vs small particle mass proposed as a more sensitive tool for this purpose. All of these techniques however suffer from the issue of defining which stages of the impactor to ratio in order to achieve satisfactory sensitivity for in vivo testing as a means of controlling the in vivo deposition of a product.

As an alternative, Principal Component Analysis (PCA) allows for modeling of full impactor distributions and reduces these profiles to typically two or three principle components, accounting for a large percentage of the variation observed.

This is an alternative means of describing APSD can be used to define the “sensitivities” of different batches of product. We propose that PCA is the most sensitive tool to detect change in the APSD profile but due to its nature is somewhat limited in deriving criteria that can be applied in a routine testing environment. As alternatives we will therefore compare both the current accepted method of Stage Groupings and the new proposal of Abbreviated Impactor Measurement – Efficient Data Analysis (AIM-EDA) to PCA in order to determine their respective ability to detect changes in product performance.

Method

A set of development data on a Pfizer Dry Powder Inhale product created using the Next Generation Impactor (NGI), containing 1990 data points was used to establish the model. The results of this analysis were as follows:

For the AIM-EDA method a plot of LPM/SPM ratio versus MMAD was created where LPM consisted of the sum of the material deposited on S1-S3 and SPM consisted of the sum of material deposited on S4-MOC. Both linear and quadratic models (Figures 3 & 4) were applied to the plot of LPM/SPM vs MMAD however there was very little difference between the two therefore the linear model was used for simplicity. A 99% prediction interval has been applied.

From the plots in Figure 3, the acceptable ranges of LPM/SPM ratio of 0.417 to 0.893 were derived based on the linear modeling of the data. Applying these acceptance criteria to the 1738 points that remained outside of the Phase Ib data the dataset generated 158 “passed” measurements and 460 “failed” measurements via the AIM-EDA approach.

An additional criteria of Impactor Size Mass (ISM), which is the sum of S1 to MOC, however must be included to remove data in which the MMAD is unchanged but the overall impactor mass has increased beyond that of the Phase Ib data. Thus a range of ISM of 21.67 to 32.17 was applied in combination with the LPM/SPM ratio which reduces the number of “passed” batches to 872 and the number of “failures” accordingly increases to 866.

Results

The numbers of Type I and Type II errors for each of AIM-EDA and Stage Groupings were compared using PCA, the standard method which each was judged.

Figure 5: PCA scores plot coloured by “Pass” or “Fail”

Figure 6: PCA scores plot coloured by AIM-EDA criteria

Figure 7: PCA scores plot coloured by Stage Groupings criteria

Conclusions

The number of Type II errors was not significantly different between AIM-EDA and Stage Groupings with both techniques giving ~5%. There was however a significant difference between AIM-EDA and Stage Groupings with regards Type I errors where AIM-EDA gave considerably fewer Type I errors than Stage Groupings. This analysis also demonstrates the potential value of Principal Component Analysis as a tool in the development of APSD control strategies.

References