

# ALTERNATIVE APPROACHES FOR MMAD DETERMINATION

(Keep it simple - Do the right thing)

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## BACKGROUND

The Mass Median Aerodynamic Diameter (MMAD) associated with quantifying aerodynamic particle size distribution is generally calculated based on a model that assumes an underlying log-normal distribution of the particle size mass. Since the particle size distribution of many products is not log-normal, alternative methods for calculating MMAD can be considered.

## INTRODUCTION

The aerodynamic diameter of an airborne drug particle is the key attribute in determining its regional deposition in the lung, which in turn is related to inhaled drug product safety and efficacy. Two particles may differ in their shape, size, and/or density and still be aerodynamically indistinguishable because they have similar behavior in a moving air stream. A cascade impactor (CI) or multi-stage liquid impinger (MSLI) is used to measure the range of aerodynamic diameters for drug particles in a pharmaceutical aerosol product.

The Mass Median Aerodynamic Diameter (MMAD), associated with quantifying the central tendency of aerodynamic particle size distributions (APSDs) of inhaler-generated aerosols, is generally calculated based on a model that assumes an underlying log-normal distribution of the mass-weighted data.

USP Chapter <601> provides a method for determining MMAD as a metric describing APSD central tendency, either graphically or computationally, assuming a log-normal distribution. The graphical approach is based on the visual fit of a straight line to data manually plotted on log-probability paper. Manual plotting of an APSD is a time consuming activity and the fit of the line to the data can be very subjective. The computational approach eliminates the subjectivity, but would typically require the use of statistical software or a spreadsheet to perform least-squares regression. In either case, if the particle size is not log-normally distributed, the MMAD determination will be biased to an unknown extent.

However, it is possible to fit the cumulative mass-weighted distribution curve to the observed data without assuming a particular underlying log normal distribution. Two such computational approaches are given here. Additionally, a simple-to-perform manual procedure based on interpolation of the two cumulative distribution points either side and nearest to the 50<sup>th</sup> mass percentile is also presented. The four approaches for determining MMAD have been evaluated for four different product types.

## METHODS

**General**  
Cumulative mass-weighted APSDs were calculated taking examples from the blinded IPAC-RS database of CI/MSLI measurements for inhaler drug products. These data included the collection stage intended to size-fractionate the largest particles that entered the impactor/impinger system, which by definition has no upper size bound. These APSD profiles were used to fit various models against the effective cutoff diameters (ECDs) assigned to the stages of the measuring system.

The USP <601> describes a method of calculating the MMAD which involves plotting the percentage of mass less than the stated aerodynamic diameters versus the aerodynamic diameter on log probability paper. The figure presented in USP <601> is an idealized size distribution which conforms to a log-normal distribution. This monograph does not provide an alternative approach when the distribution is not log-normal. If there are significant deviations from log-normality, performing a linear regression over the entire dataset could result in significant bias depending where and by how much mass deviates from log-normality occur. One solution to the problem is the use of mathematical algorithms that are able to fit the S-shaped (sigmoidal) curves frequently encountered with inhaler-generated APSD data. Two such algorithms [references] were used to calculate MMAD.

**USP <601> Log-Normal Model**  
Normal probability z-scores were calculated for each cumulative proportion for the "standard" approach for MMAD determination, as outlined in USP <601>. Linear least-squares regression was used to fit the z-scores to the log<sub>10</sub> of the CI/MSLI ECDs. The largest sizing stage, which has a cumulative proportion of 1, is not used in the model fitting with this approach, since the z-score for 1 is infinity. MMAD was determined by back-solving the fitted data for the size corresponding to the 50<sup>th</sup> mass percentile using Equation (1) with  $\mu$  and  $\sigma$  from the linear regression. The fitted line was transformed back into original scale ECDs for comparison to other fitted models.

$$MMAD = 10^{\frac{(\sigma \cdot Z) + \mu}{\sigma}} \quad \text{Equation (1)}$$

**Mercer-Morgan-Flodin and Chapman-Richards Models**  
MMAD was also determined using two non-linear regression models, Mercer-Morgan-Flodin and Chapman-Richards, given in Equations (2) and (3), respectively to fit the observed data to a sigmoid curve.

$$Y = (ab + cx^d)^e / (b + X^d) \quad \text{Equation (2)}$$

$$Y = a(1 - b \exp(-cx))^{1/d} \quad \text{Equation (3)}$$

SAS v9 PROC NLIN was used with the Gauss-Newton iterative method specified, and appropriate starting values were determined to ensure convergence.

### Two-Point Manual Interpolation

A fourth approach was also used to estimate MMAD, based on linear interpolation between the nearest data points either side of the cumulative 50<sup>th</sup> mass percentile value. This was accomplished with a simple algebraic calculation, not requiring least squares regression.

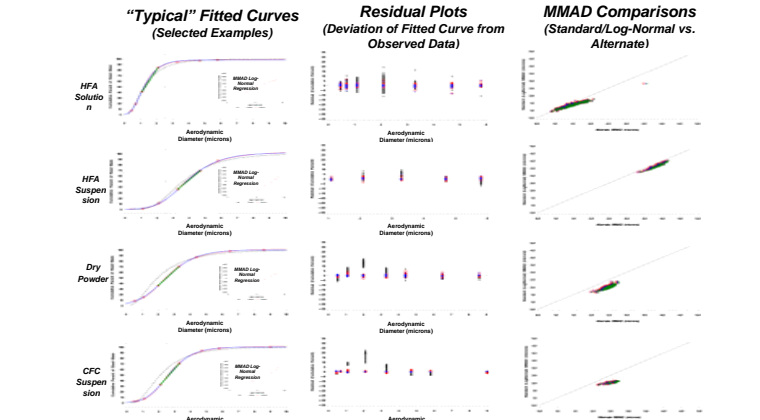
## RESULTS

Plots of fitted curves, residuals (deviations of the fitted curves from observed data) and comparisons of MMADs from the standard (log-normal) versus the three alternative approaches are presented in the middle panel.

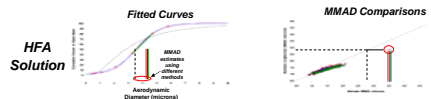
Table 1 provides summary results of MMAD calculations using the different approaches.

## Comparison of MMAD Approaches for Different Products

MMAD Calculated by Different Methods:  
Standard/Log-Normal (Black), Morgan-Mercer-Flodin (Red), Chapman-Richard (Blue),  
2-Point Interpolation (Green)



### Extreme Value Example



**Table 1 - Summary of MMAD Calculations**

	MMAD USP <601>	MMAD MMF	MMAD CR	MMAD 2-Point Interpolation
HFA Solution (n=201)	Mean 1.36 Median 1.38	1.46 1.45	1.48 1.47	1.51 1.53
HFA Susp (n=80)	Mean 3.65 Median 3.65	3.80 3.82	3.83 3.85	3.88 3.90
Dry Powder (n=279)	Mean 2.02 Median 2.02	2.43 2.44	2.47 2.48	2.51 2.52
CFC Susp (n=43)	Mean 2.03 Median 2.05	2.48 2.52	2.51 2.56	2.55 2.59

## DISCUSSION

As can be seen from examples of fitted curves and residual plots, APSDs for the HFA solution MDI group, although containing some minor deviations from ideal, appear to conform closest to a log-normal distribution. Larger deviations from log-normality are evident with the other products, in particular the dry powder inhaler and CFC suspension MDIs groups. Given these systematic deviations, it follows that performing a linear regression over the entire dataset could result in increasing bias by an extent depending where precisely these deviations occur. Furthermore, giving an equal weighting to the extremes of the distribution where very little drug is recovered compared with the central portion of the APSD will amplify precision-related error in the calculated MMAD due to assay variability.

This broad assessment across the major inhaler types revealed that MMAD estimates using the USP method may be offset by as much as 0.5 microns compared with the three alternative methods which by contrast were in good agreement. If it is assumed that the true MMAD values will be better captured by methods that avoid an underlying assumption of a model distribution form, it follows that the simple algebraic derivation of MMAD by interpolation between the two data points closest and either side of the 50<sup>th</sup> mass percentile is more accurate than the USP method.

## CONCLUSIONS

- Many of the examples taken from the IPAC-RS cascade impactor database indicate that APSDs of inhalation aerosols are not log-normal;
- Linear regression of the entire dataset derived from a log-probability plot of the APSD (USP method) results in relatively large deviations in MMAD estimates when compared to the outcome from algorithms that take into account the sigmoidal shape of these APSDs. This outcome is the result of visible deviations from log-normality apparent at either extreme of these APSDs, also associated with little drug mass;
- MMADs determined by the 2-point manual interpolation approach are very consistent with MMADs obtained from more complex non-linear fitting approaches and in the philosophy of "keep it simple - do the right thing", should be the preferred method.
- This simplified approach is also consistent with that for CI-based APSD assessment in ISO/FDIS/27427:2000 "Anaesthetic and Respiratory Equipment - Nebulizer Systems and Components".

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