Statistical Techniques Used in Simulation of Particle Size Distribution Profiles of Orally Inhaled Products

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Abstract

The FDA classifies statistical methods for assessment of in vitro bioequivalence tests for orally inhaled products (OIPs) as either profile or non-profile analysis. Profile analysis related to the drug particle size distribution (PSD), commonly measured by cascade impactor, is one of the critical attribute tests previously and currently being considered by the FDA, in which profile comparisons between test and reference products are based on chi-square differences. An adequate assessment of profile comparison methods prompted efforts to generate realistic simulated cascade impactor profiles which take into account the mean, the variance and the inter-site correlation of mass recoveries between cascade impactor deposition sites. However, much observed profile data do not appear to follow a multivariate normal distribution, imposing significant challenges to simulating the inter-site correlations. This talk discusses considerations and approaches for methods that can be employed to transform the observed profile data into an approximately multivariate normal distribution using examples which realistically mimic the non-normal mass distribution exhibited by many OIPs.

Key Words: multivariate normal distribution, particle size distribution, statistical simulation

1. Introduction

The FDA classifies statistical methods for assessment of in vitro bioequivalence tests for orally inhaled products (OIPs) as either profile or non-profile analysis. Profile analysis related to the drug aerodynamic particle size distribution (APSD) is one of the key in vitro tests for supporting bioequivalence between test (T) and reference (R) products for OIPs. APSD profile assessment (a multivariate response) is assessed through Anderson cascade impactor (CI) testing.

Effective comparison of CI profiles of T and R products requires a method with good statistical properties and ability to detect differences that are considered to be of practical importance. FDA proposed the chi-square ratio statistic (CSRS) to test equivalence between T and R products in their June 1999 draft guidance. This test does not rely on any underlying distributional assumption. The PQRI Profiles Comparison Working Group concluded that the FDA proposed test performed consistently with the stated expectations for statistical properties but could not effectively discriminate between CI profiles with certain differences of practical importance. The FDA continued work internally and subsequently proposed a modified chi-square ratio statistic (mCSRS) which has improved ability to detect important differences.

2. Methods

2.1 Motivation

The performance capability of the modified chi-square test is currently being assessed, which requires simulation of realistic CI profiles. Simulations based on mean and variance of stage recoveries, assuming independence among the stages, does not effectively mimic important characteristics of the real data. Simulation modeling which includes stage-to-stage correlation consistent with underlying APSD mechanisms, in addition to the mean and variance of stage recoveries can provide simulated data which closely matches real data. However, if observed profile data do not follow a multivariate normal distribution it imposes significant challenges to simulating the inter-site correlations and generating realistic profile characteristics.

Some of the challenges are: Transformation of real (non-normal) data into an appropriate normal distribution space to allow use of standard simulation techniques, and Back-transformation of simulated data which has desired characteristics of original data.

2.1.1 Example of Cascade Impactor Data

An example of a typical CI data for three profiles is given in Table 1 and the corresponding figure is given in Figure 1.

Table 1: Example Data for Three Profiles

Product	*Act*	*Throat*	*S0*	*S1*	*S2*	*S3*	*S4*	*S5*	*S6*	*S7*	*Filter*
Profile1	14.28	38.26	1.83	2.06	2.24	7.56	17.97	13.11	1.59	0.51	0.57
Profile2	18.56	46.32	2.15	0.43	0.92	9.11	12.00	7.11	2.44	0.82	0.14
Profile3	19.22	47.51	2.03	0.82	0.83	9.06	10.21	7.15	2.01	0.94	0.20

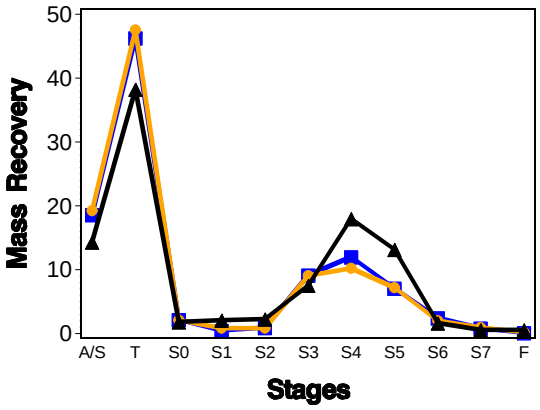

Figure 1: Example of three different APSD profile

2.1.2 Example of blinded actual CI Profiles

The mCSRS algorithm takes 30 Test and 30 Reference CI tests. An example of 30 CI profiles of blinded actual CI data in which Stage 2 exhibits an extreme value, indicating likely non-normal distribution for that stage is shown in Figure 2.

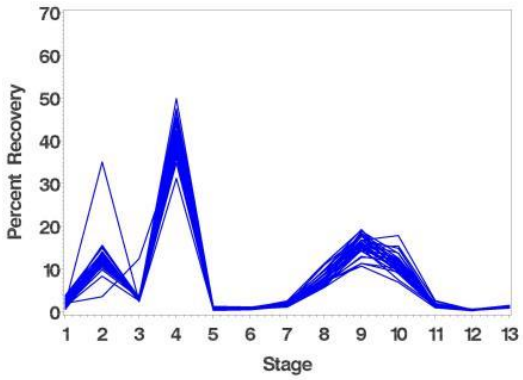

Figure 2: Actual blinded APSD profile

2.1.3 Simulated Profile with No Transformation

If the mean and covariance structure are used to simulate 30 profiles assuming multivariate normal distribution:

- Simulated profile does not adequately mimic original profile at Stage 2
- Transformation of the original profile might be necessary to simulate realistic profile data.

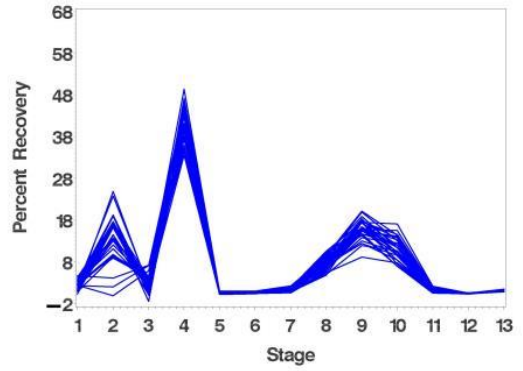

Figure 3: Simulated APSP profile with no transformation

2.2 Transformation

When the observed data is not normally distributed, and especially when there are outliers in the observed data, a transformation to more closely approximate a normal distribution is needed before simulation. Several transformations were considered and two of the methods and their results are illustrated below.

2.2.1 Probit Transformation

The Probit Transformation technique is illustrated in Figure 4. The step function is the empirical cumulative density function of recovery at a particular CI stage which is mapped to an appropriate normal cumulative density function to define the transformation needed to be applied to the actual recovery values for that stage of each of the CI profiles.

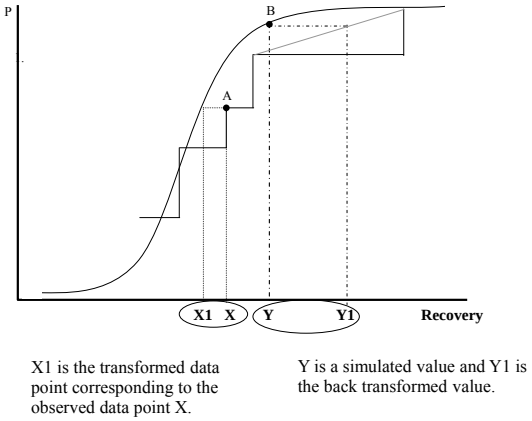

Figure 4: Simulated APSP profile with no transformation

2.2.2 Box Cox Transformation

Box Cox Transformation follows the form of:

$$f(x) = \begin{cases} x^{\lambda}, & \lambda \neq 0 \\ \ln(x), & \lambda = 0 \end{cases}$$

3. Results

3.1 Probit transformation on Bi-Modal Data

Transformed data is much closer to a true normal distribution simplifying the simulation process steps:

- Simulation for a multivariate normal is performed using the mean vector and covariance matrix calculated from the transformed data.
- The simulated data is back transformed to the original scale using an inverted probit transformation algorithm.

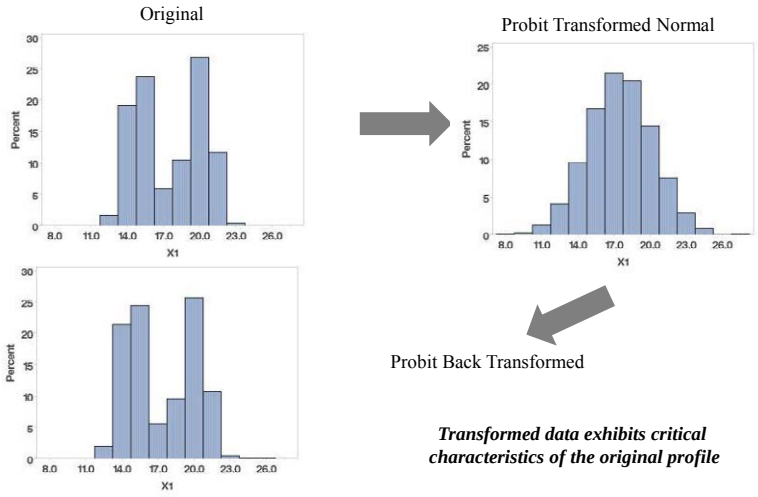

Figure 5: Example of Probit Transformation with Bi-Modal Data

Probit Transformation might be beneficial and improve the simulation results when there is indication of important deviation from normality (e.g. using Q-Q plots) at any CI stage.

3.2 Box Cox Transformation on Bi-Modal Data

As seen in Figure 6, the Box Cox transformation does not mimic the original distribution.

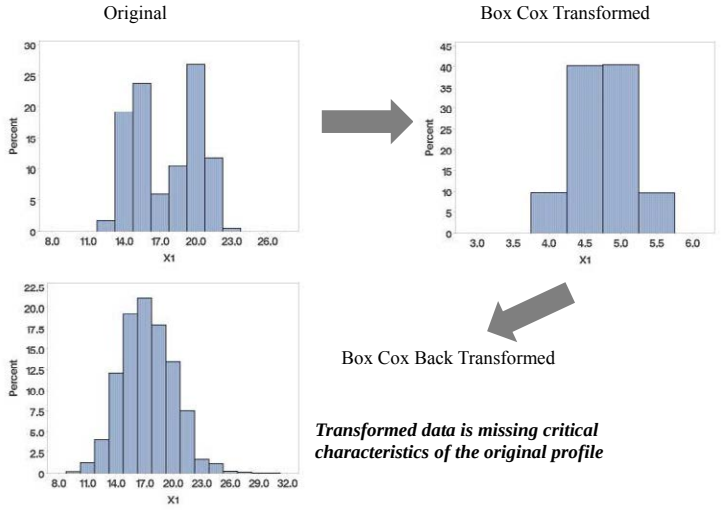

Figure 6: Example of Box Cox Transformation with Bi-Modal Data

3.3 Probit Transformation on Simulated CI Data

As seen in Figure 7, the simulated profiles using the Probit transformation in Figure 7, mimics the original profile, especially Stage 2.

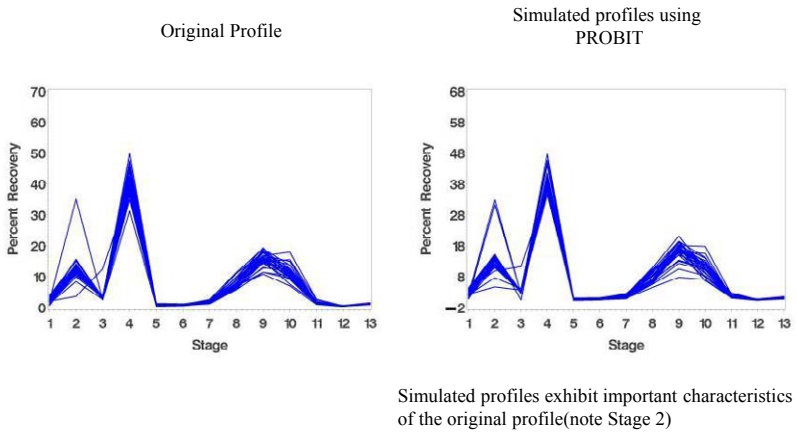

Figure 7: Example of Simulated APSD Profile using Probit Transformation

3.4 Box Cox Transformation on Simulated CI Data

The Box Cox Transformation does not do a good job on replicating the original profile, when there is an extreme value present in Stage 2. This is illustrated in Figure 8.

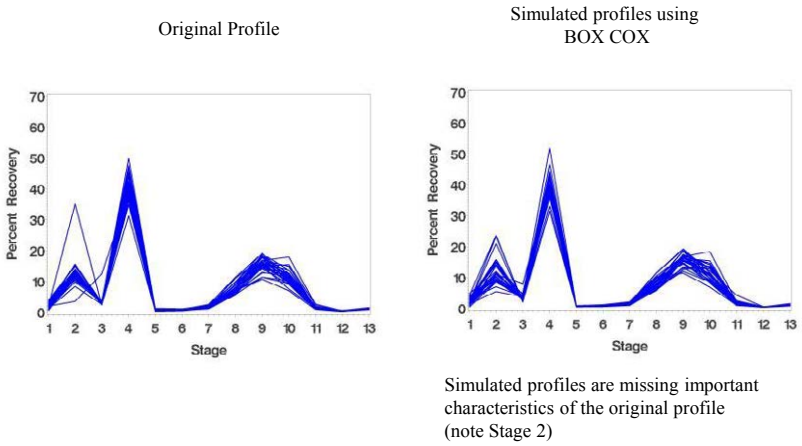

Figure 8: Example of Simulated APSD Profile using Box Cox Transformation

3.5 Simulated Stage 2 Data

The Stage 2 data of 30 CI profiles is taken and transformation is done using Probit transformation. As seen in Figure 9, the Probit back transformed data mimics the original Stage 2 data pretty well.

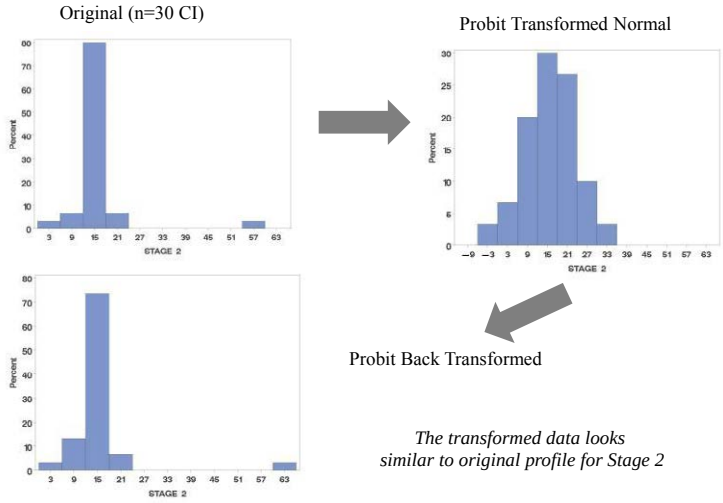

Figure 9: Example of Probit Transformation with actual blinded Stage 2 Data

The same data is used to do a Box Cox transformation and as seen in Figure 10, the back transformed data does not replicate the original Stage 2 data.

3.6 Comparison of Means and Standard Deviation on Stage 2 Simulated Data

1000 groups of 30 CI profiles were generated for the Stage 2 data. The Probit and Box Cox transformations are applied. The distributions of the means for the 1000 groups using both these transformations are shown in Figure 11 .

The comparisons of the distributions of the standard deviations for the 1000 groups using the Box Cox and Probit transformations are shown in Figure 12.

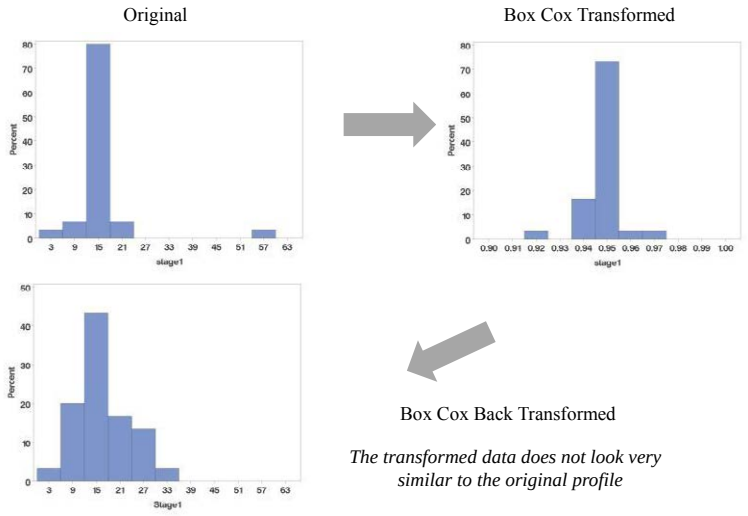

Figure 10: Example of Box Cox Transformation with actual blinded Stage 2 Data

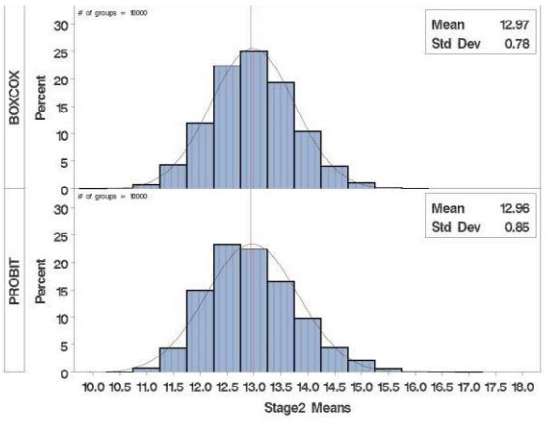

Figure 11: Distribution of the Means of Stage 2 data

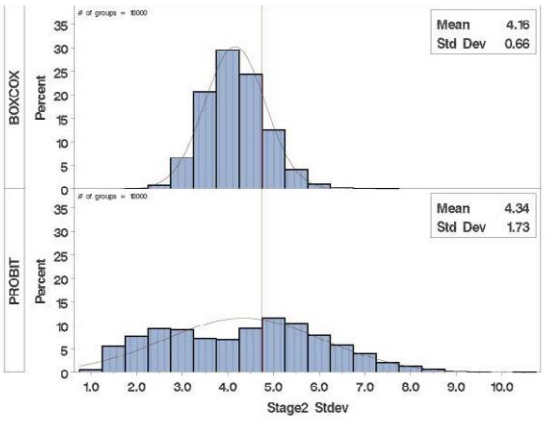

Figure 12: Distribution of the Standard Deviations of Stage 2 Data

4. Summary

If the original distribution follows a multivariate normal distribution, then mean vector and covariance matrix can be directly calculated from the observed data for simulation purposes.

If data is not normally distributed and especially when there are outliers in the observed data, a transformation might be necessary. Several transformation techniques, such as Box Cox transformation were tried. We faced difficulties in back-transforming simulated data from some transformations into the original scale.

The PROBIT transformation works well in approximating the original profile.
The simulation should be based on the mean vector and covariance matrix from the transformed data. The simulated data is then transformed back to the original scale to use in mCSRS tests.

Acknowledgements

The authors thank the IPAC-RS group.

References

Christopher and Dey (2011) "Detecting Differences in APSD: Efficient Data Analysis (EDA) vs. Stage Grouping", RDD Europe 2011, Vol1, pp 215-224.

FDA Draft Guidance for Industry (first draft 1999, second draft 2003) “Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action”

Pan Z., Christopher, J D, Lyapustina, S and Chou, E. (2004) “Statistical Techniques Used in Simulation of Cascade Impactor Particle Size Distribution Profiles”, Respiratory Drug Delivery IX, pp 669-672.

Weber et al. (2012) “A Stability Analysis of a Modified Version of the Chi-Square Ratio Statistic: Implications for Equivalence Testing of Aerodynamic Particle Size Distribution”, The AAPS Journal, Published Online: 25 September, 2012.

Yi Tsong (2000) “Comparative Statistics for Assessing In-vitro Equivalence Based on Profile Measures”, OINDP Advisory Subcommittee Meeting on FDA Guidance on Drug Products for Oral Inhalation and Nasal Delivery.