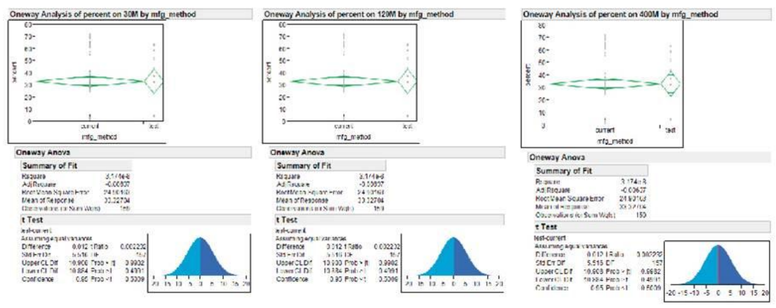
Efficient Analysis of Particle Size Distributions With JMP Non-Linear Models

Rob Lievense, Tanya Davis, Raj Thota, Jack Irwin, Carlos Paz

Perrigo Company R&D, Allegan, MI 49010

Introduction: Particle size distribution (psd) analyses are typically used for solid drug products as physical characteristics and are related to critical quality attributes (CQA) for the end dosage form. Mesh screen testing offers immediate information for a given batch; however, analysis of such data can be incomplete due to focus on weight left on "target" screens. Expanded screen testing and analyses with the non-linear modeling tools offer comprehensive psd trending without the need for more complex analytical devices. The tools were used to determine if an intermediate powder, manufactured with two different manufacturing methods, had equivalent particle size distributions.

Previous Analysis Methods: Target screens (30M, 120M, and 400M) are established and the mean cumulative amount of material left on a given screen is compared by the manufacturing method category via t-tests.

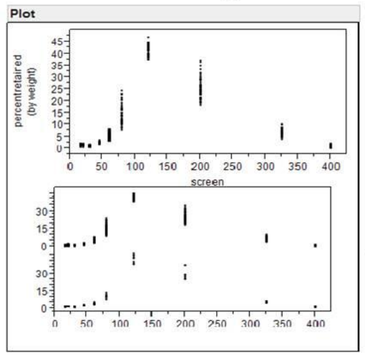


The analysis is subject to error due to the following issues:

- Screens are incorrectly treated as independent variables
- The model fit for the target screen results is poor to very poor (r-square: 8% to 24%)
- The summary analysis incorrectly concludes significant evidence of differences between manufacturing methods.

Subject Analysis Method: The non-linear modeling tools in JMP offer a comprehensive comparison of the particle size distributions for the two groups. The dependent nature of the screens is effectively handled in the analysis and statistical error is minimized.

Results: The model is set up with the percent weight as a response (y), screen size as a predictor (x), and the manufacturing code as the group.



The plot clearly illustrates a peaked shape with differing rates of change in % weight between screens would likely fit the data for the groups.

Model Comparison

Model	AICc	AICc Weight	BIC	SSE	MSE	RMSE	R-Square
Gaussian Peak	2677.0916	1	2706.7872	4718.7358	9.0052211	3.0008701	0.9481287
Quintic	2729.7752	3.63e-12	2784.6171	5090.501	9.827222	3.13484	0.944042
Lorentzian Peak	2764.7288	9.329e-20	2794.4244	5567.2107	10.624448	3.2595165	0.9388017

Comparison of a few models available in JMP illustrates a very good fit of the Gaussian Peak model to the particle size data as the best to use for the psd. The model includes three parameters, which can be compared to determine if evidence exists of statistical equivalence between the manufacturing groups.

Prediction Model

$$a * \mathrm{Exp}\left[-\left(0.5 * \left(\frac{(\mathrm{screen} - b)}{c} \right)^2 \right) \right]$$

a = Peak Value

b = Critical Point

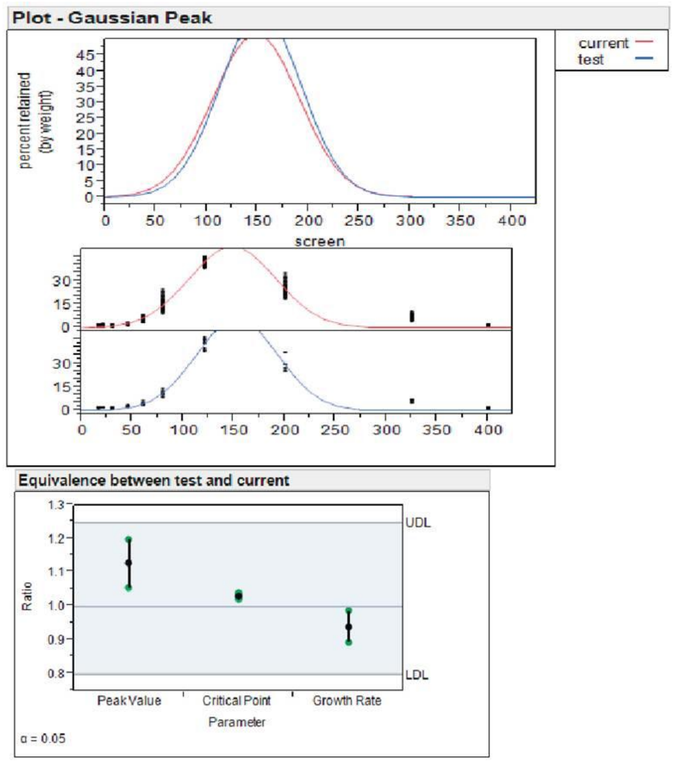
c = Growth Rate

The math formula of the predication model used illustrates the 3 parameters. The table of actual values with 95% confidence intervals for the manufacturing methods (*code*) is shown.

Parameter Estimates

Parameter	Group	Estimate	Std Error	Lower 95%	Upper 95%
Peak Value	current	51.861442	0.6970579	50.495234	53.22765
Critical Point	current	148.14048	0.4115512	147.33385	148.94711
Growth Rate	current	42.602652	0.4424241	41.735517	43.469787
Peak Value	test	58.507282	2.1413176	54.310376	62.704187
Critical Point	test	152.761	0.8203756	151.15309	154.3689
Growth Rate	test	40.069583	1.1335308	37.847904	42.291263

A comparative plot of psd for the two manufacturing methods (*code*) illustrates an excellent fit of the Gaussian Peak model. The plot illustrates overlaying curves; however, the equivalence test allows for a comparison of each of the three model parameters.



The peak values differ slightly; however, well within the upper and lower decision levels. The ratio of differences of the test group compared to the current is established through a 95% confidence level. The equivalence test plot is an easily understood graphic, which clearly illustrates the equivalence of the two methods with parameter intervals that are within the blue zone.

Conclusion: The particle size distributions of the test manufacturing process and the current manufacturing process are statistically equivalent. The test group adds value to the drug manufacturing process as it is less time consuming as well as less resource intensive. Follow up testing of the critical quality attributes (CQA) associated with psd of the drug product confirmed that the results of the process groups are equivalent. The JMP tools coupled with the routinely used screen testing equipment provide a fast and reliable prediction method for psd analysis, which supports continuous improvement in the manufacturing of solid drug products.

Acknowledgements: Thanks to the support of the visionary managers of Perrigo Global Scientific Affairs for providing needed support and resources as we continue to improve our development efforts through expanded use of JMP.

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