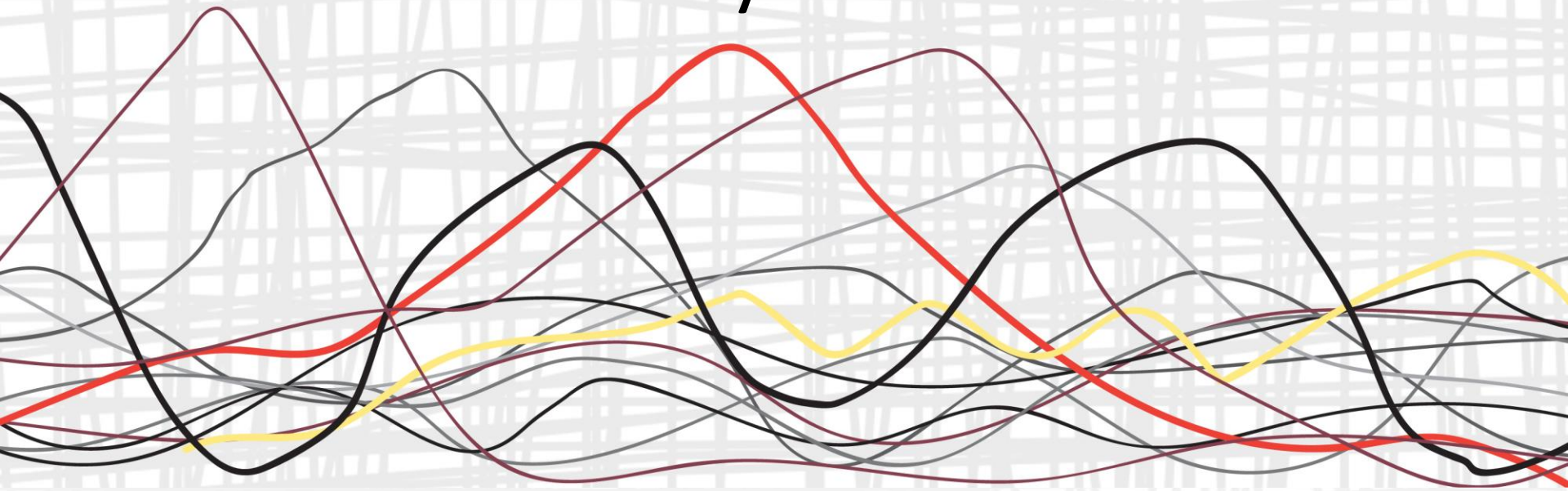
statgraphics 19®

Analyzing Data from Stability Studies



Stability Studies

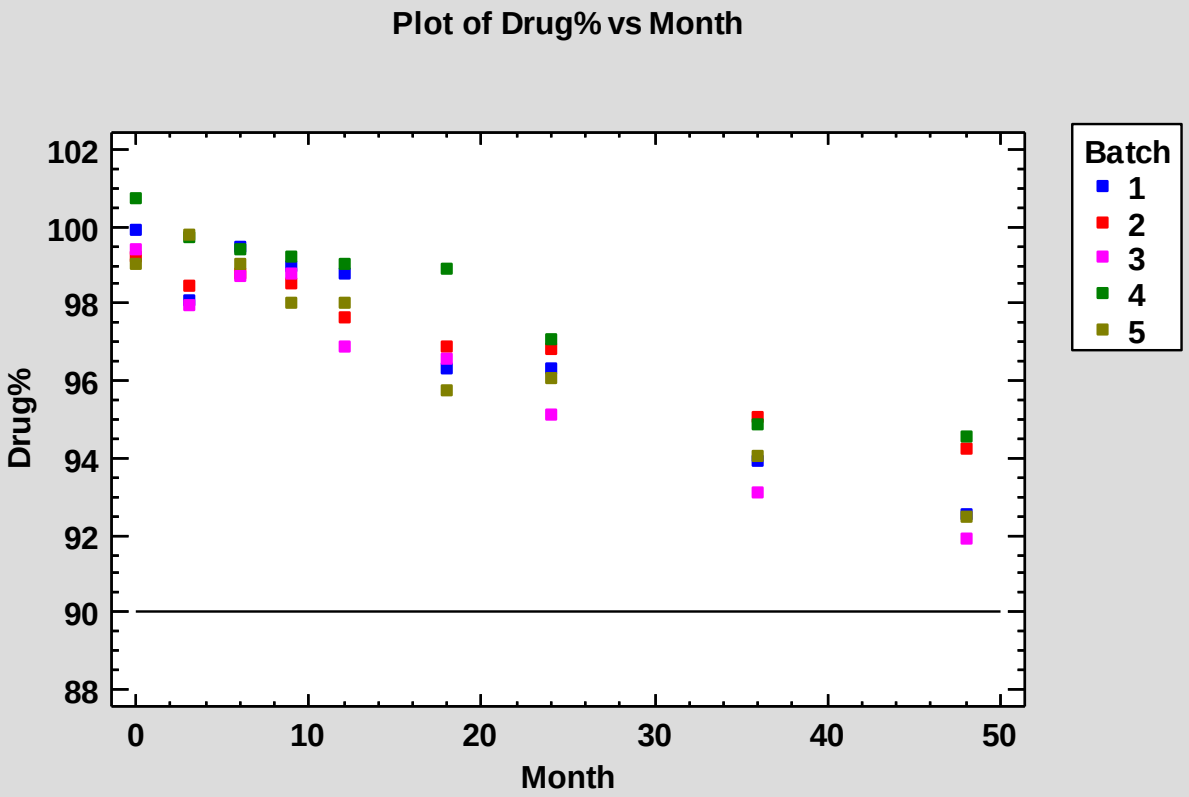
- Model how a product or component of a product varies with time
- Used to establish a shelf life or retest period for the product or component
- Common use is to model the degradation of a drug product or substance

Sample Data

Data file: *shelf life study.sgd*

- **Dependent variable:** percent of label-claimed active ingredient strength of a drug
- **Sample size:** measurements made on 5 batches
- **Sampling times:** 0,3,6,9,12,18,24,36,48 months after production
- **Lower specification limit:** 90%

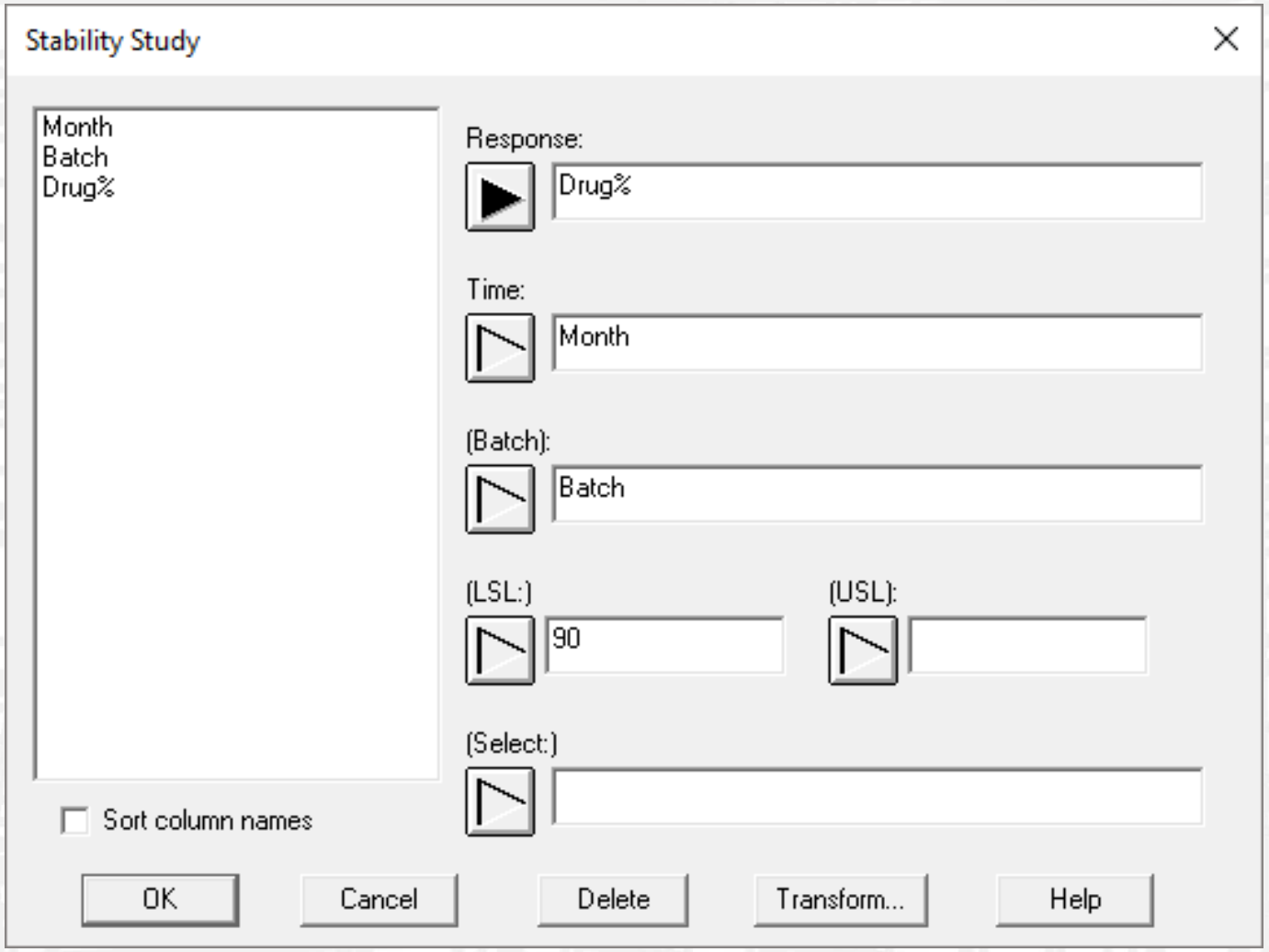
Plot of Sample Data



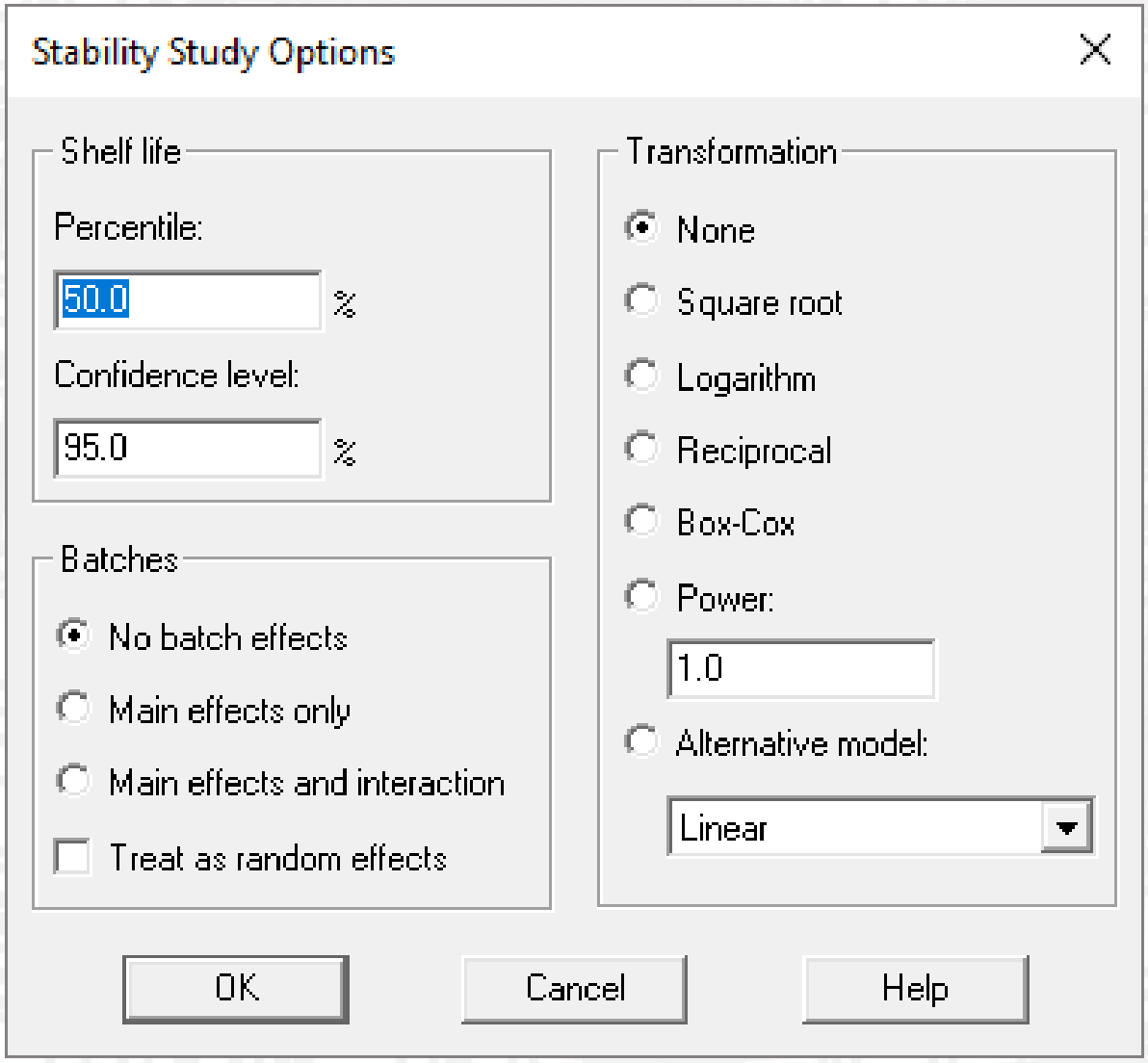
Basic Approach to Establishing Shelf Life

- Model the degradation of drug strength over time. A linear or nonlinear model may be used.
- Create a lower prediction limit for a specified quantile of the distribution of observed measurements at each point in time. Often P50 (mean) is used.
- Find the intersection of the prediction limits with the specification limit.
- If there are significant differences between batches (assuming fixed effects), create prediction limits for each batch and select the minimum prediction limit at each point in time.

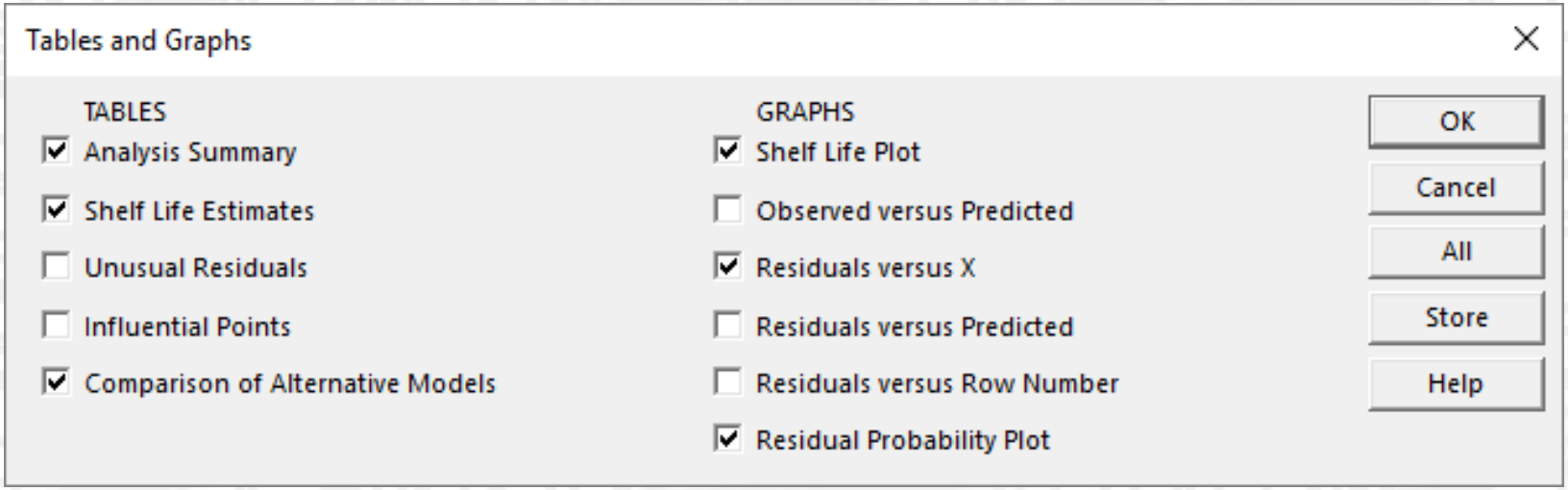
Data Input Dialog Box



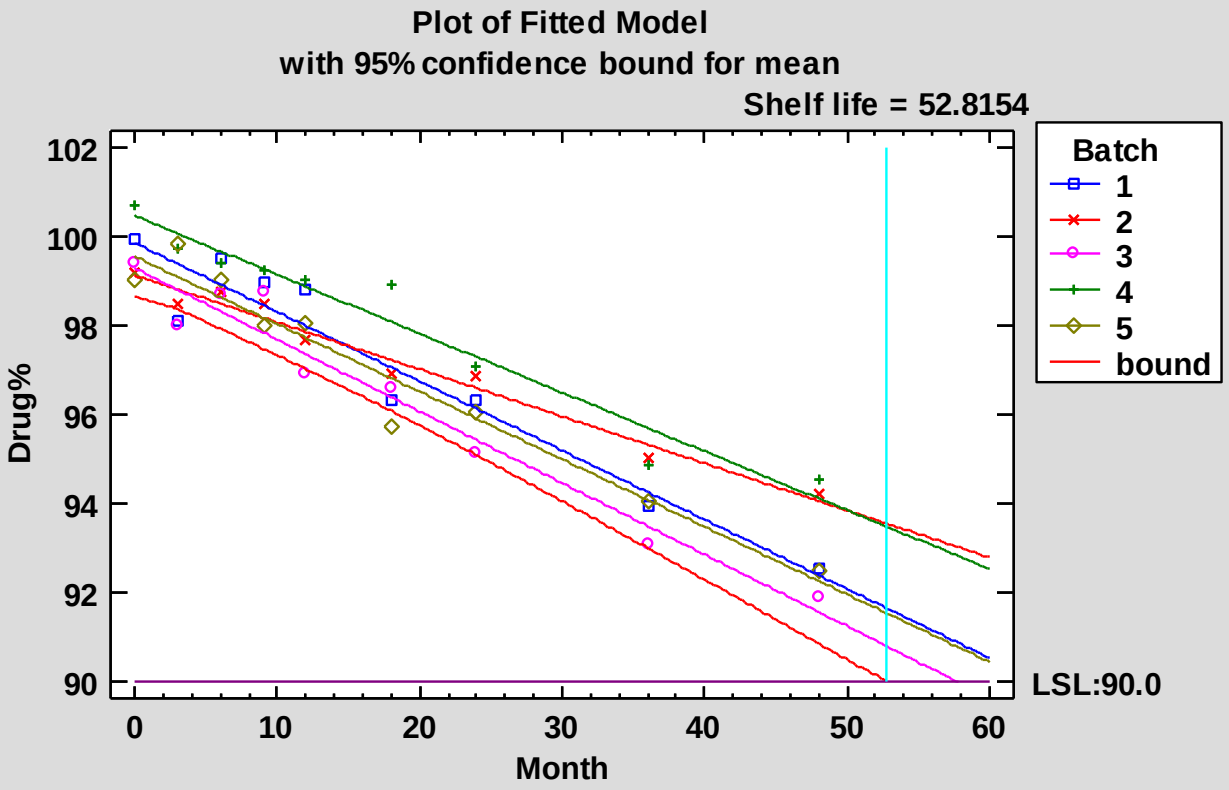
Analysis Options Dialog Box



Tables and Graphs



Fitted Model



How should batches be handled?

- Fixed batches
  - Fit a model with different intercepts and slopes for each batch.
  - Simplify the model if batch slopes and/or intercepts are not significantly different.
  - Determine the shelf life for each batch and select the minimum shelf life as the final result.

- Random batches
  - Fit a model with additional variance components for batches and batch*time interactions.
  - Remove batch*time interactions and/or batch components if not statistically significant.
  - Determine a single shelf life based on the fitted model.

Tests for Fixed Batch Effects

Further ANOVA for Variables in the Order Fitted

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
Month	205.467	1	205.467	667.09	0.0000
Batch	13.7174	4	3.42934	11.13	0.0000
Month*Batch	4.22242	4	1.0556	3.43	0.0182

- **Month*Batch:** tests whether slopes of the batches are significantly different from each other. FDA suggests using $\alpha = 0.25$.
- **Batch:** tests whether intercepts of the batches are significantly different from each other.
- Use backward stepwise approach when deciding whether to remove terms.

Estimated Parameters

Regression Models

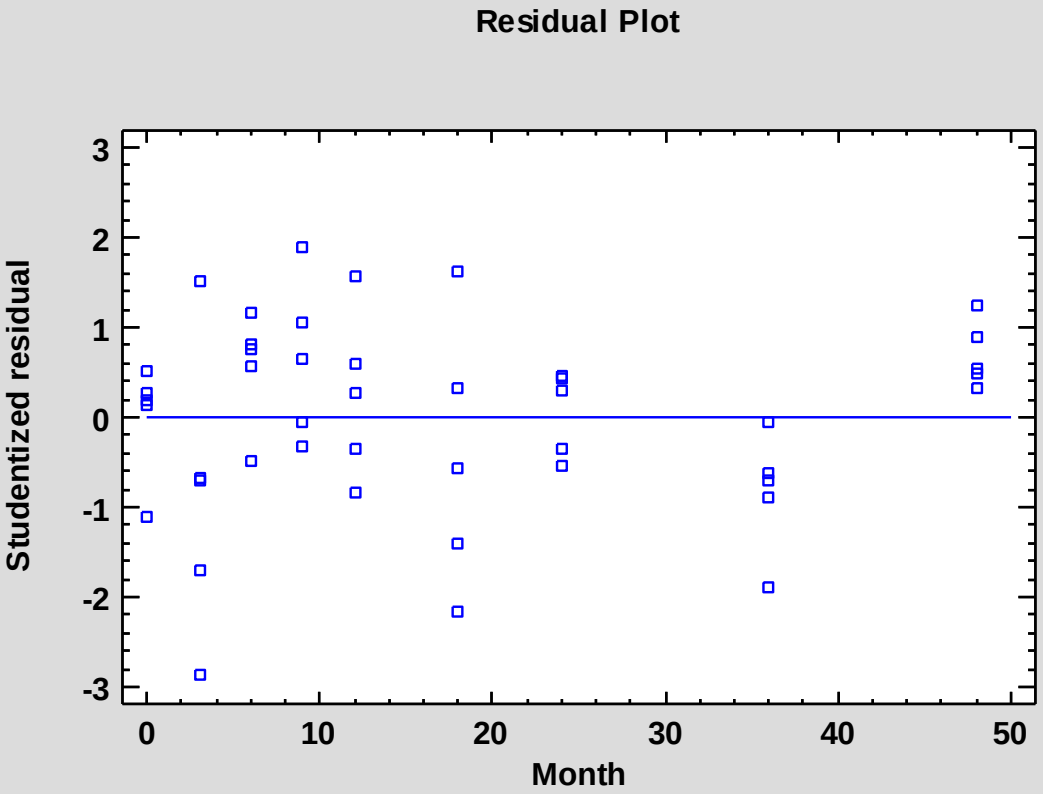
Batch	*Intercept*	*Slope*
1	99.8528	-0.155297
2	99.1239	-0.105497
3	99.2827	-0.160687
4	100.459	-0.132098
5	99.5435	-0.151586

Shelf Life Estimate

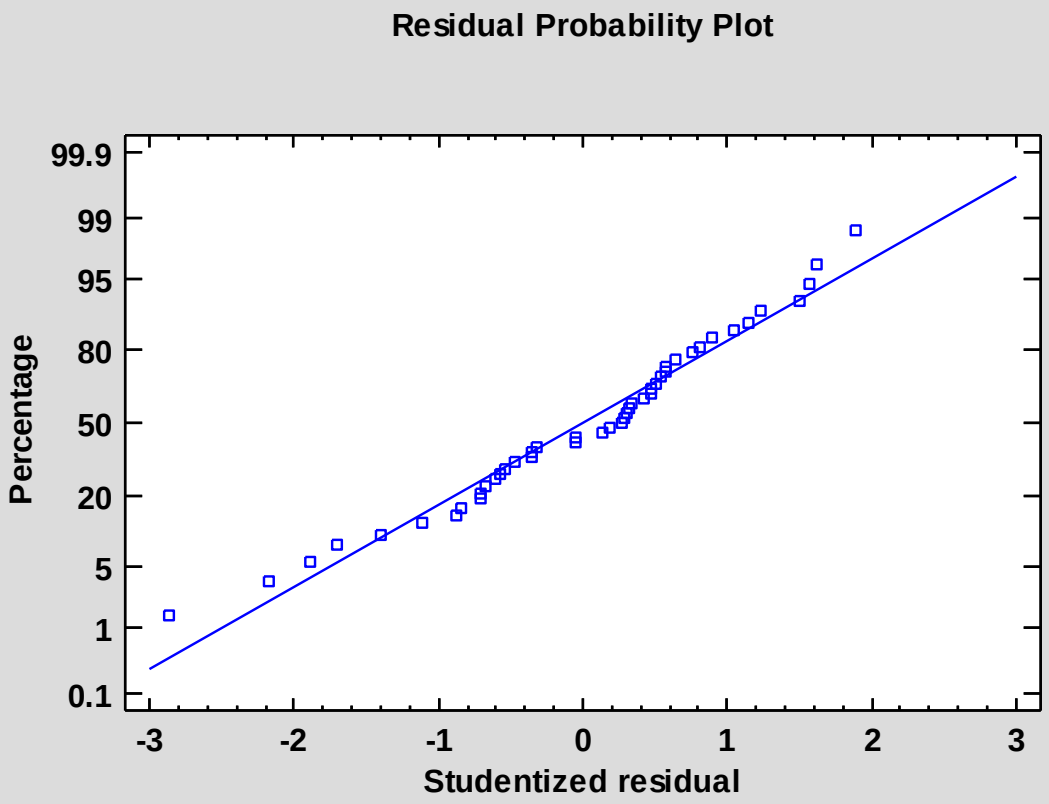
Shelf Life Estimates

Batch	*Shelf life*	*Limit*
1	52.4836	lower
2	67.6797	lower
3	47.7013	lower
4	64.5984	lower
5	51.8079	lower
Combined	47.7013	lower

Residuals versus X



Residual Probability Plot



Comparison of Alternative Models

Comparison of Alternative Models

Model	*R-Squared*	*Adj. R-squared*
Reciprocal-Y	95.68%	94.57%
Exponential	95.55%	94.40%
Square root-Y	95.47%	94.31%
Linear	95.40%	94.21%
Squared-Y	95.23%	94.01%
Reciprocal-Y squared-X	88.63%	85.70%
Logarithmic-Y squared-X	88.09%	85.02%
Square root-Y squared-X	87.81%	84.68%
Squared-X	87.54%	84.34%
Squared-Y square root-X	87.19%	83.89%
Double squared	86.98%	83.64%
Square root-X	86.95%	83.60%
Double square root	86.83%	83.44%
Logarithmic-Y square root-X	86.71%	83.29%
Reciprocal-Y square root-X	86.45%	82.96%
Logarithmic-X	<no fit>	
Square root-Y logarithmic-X	<no fit>	
Multiplicative	<no fit>	
Reciprocal-Y logarithmic-X	<no fit>	
Squared-Y logarithmic-X	<no fit>	
Reciprocal-X	<no fit>	
Square root-Y reciprocal-X	<no fit>	
S-curve model	<no fit>	
Double reciprocal	<no fit>	
Squared-Y reciprocal-X	<no fit>	
Logistic	<no fit>	
Log probit	<no fit>	

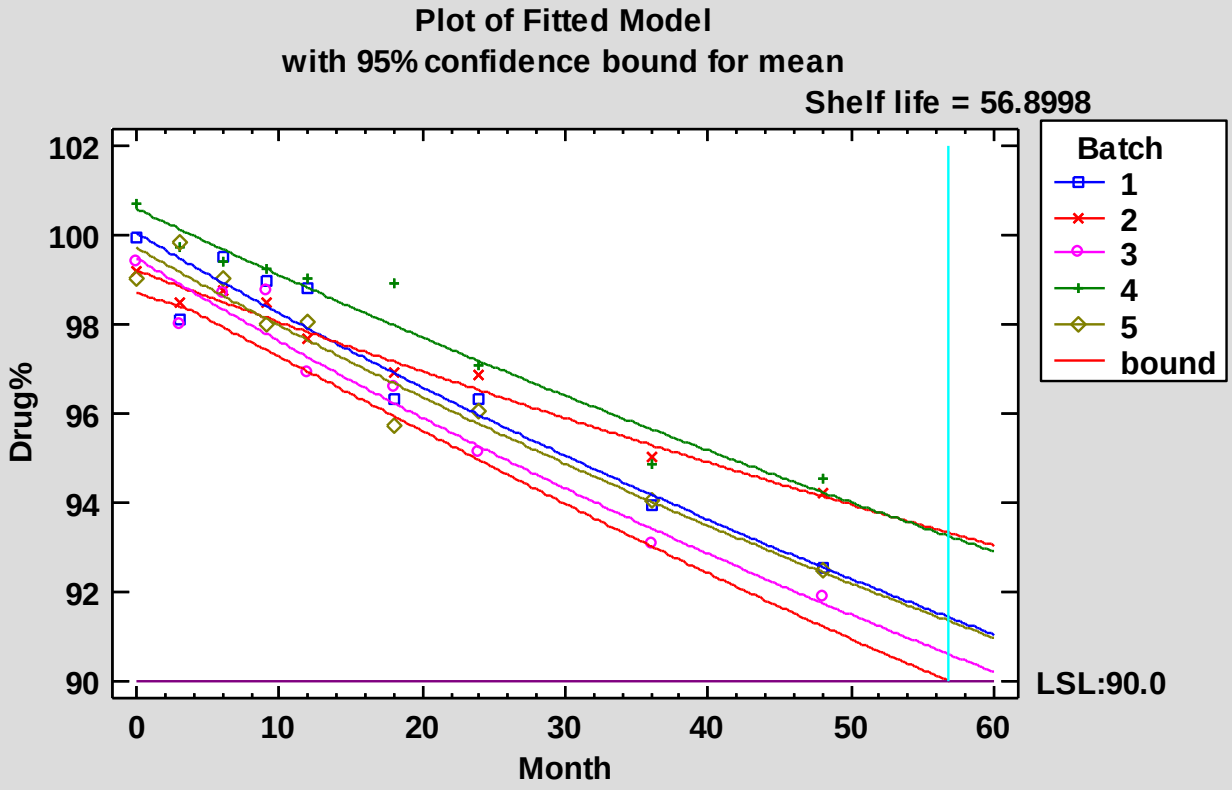
Box-Cox Transformation

- Considers models in which Y^p is a linear function of X.
- Searches for the optimal value of *p*.
- In this case:

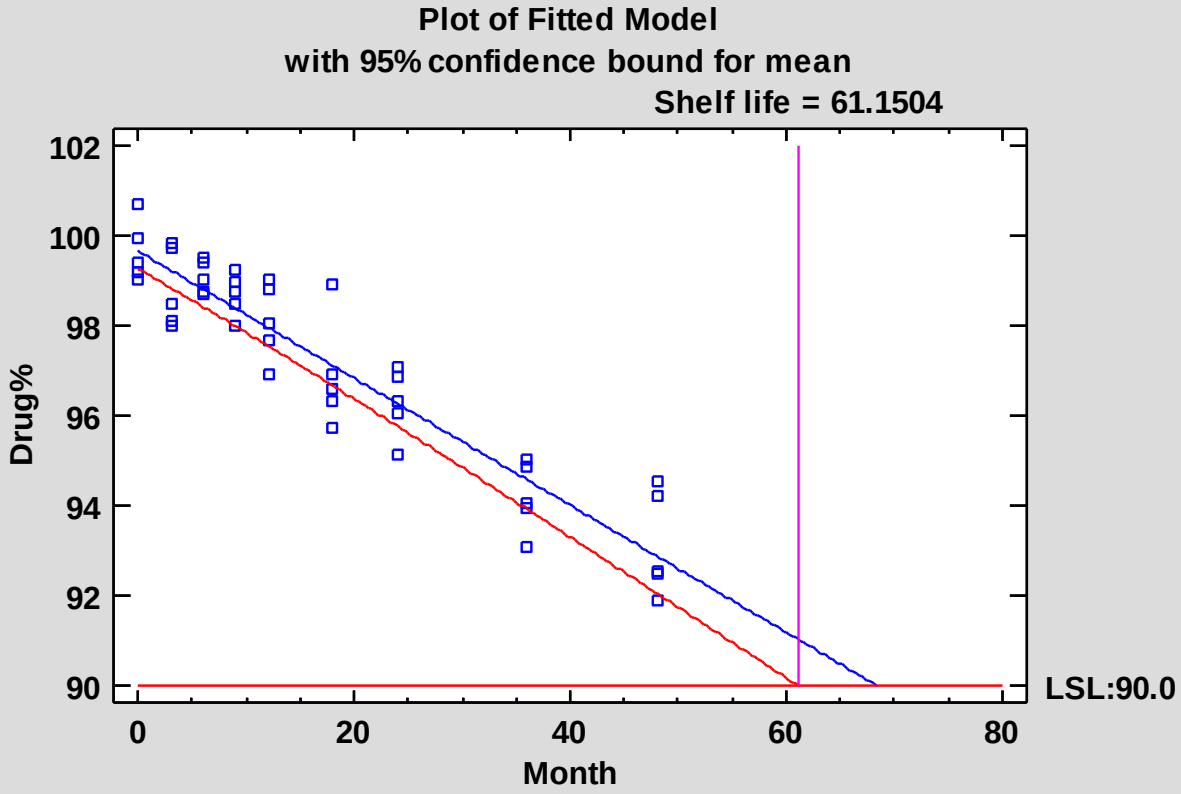
Transformation: BoxCox(-3.65)
Terms in model: Month, Batch, Month*Batch

R-squared = 95.9686 percent
R-squared (adjusted for d.f.) = 94.9319 percent

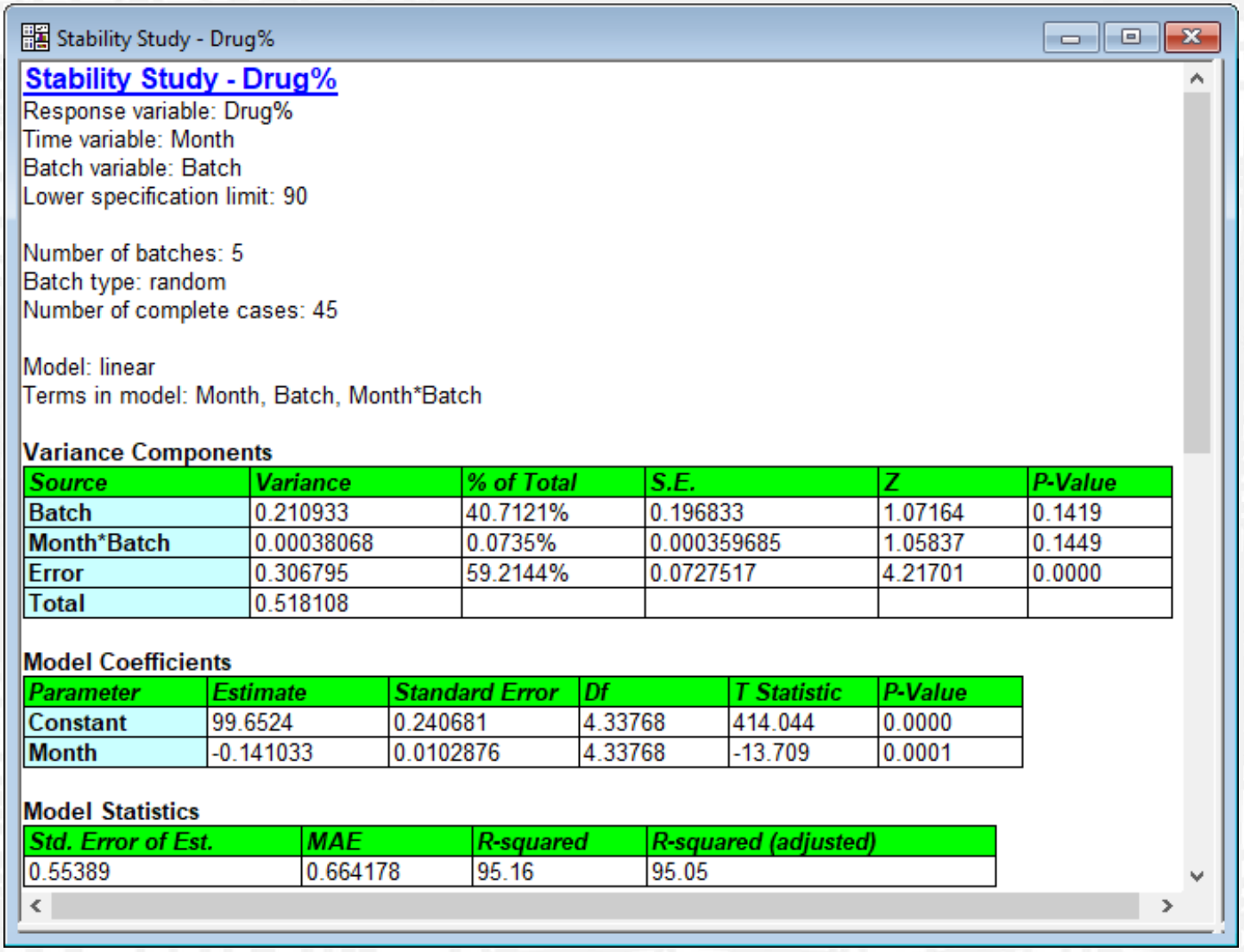
Box-Cox Model



Random Batch Effects Model



Components of Variance



More Videos

Videos are available to learn more about each of the features in Statgraphics.

You'll find them at:

www.statgraphics.com/instructional_videos

Also check our website for upcoming webinars.

References

- Chow, S. (2007). *Statistical Design and Analysis of Stability Studies*.

- U.S. Department of Health and Human Services, Food and Drug Administration, (2003). *Guidance for Industry, Q1A(R2) Stability Testing of New Drug Substances and Products*.

- U.S. Department of Health and Human Services, Food and Drug Administration, (2004). *Guidance for Industry, Q1E Evaluation of Stability Data*.