

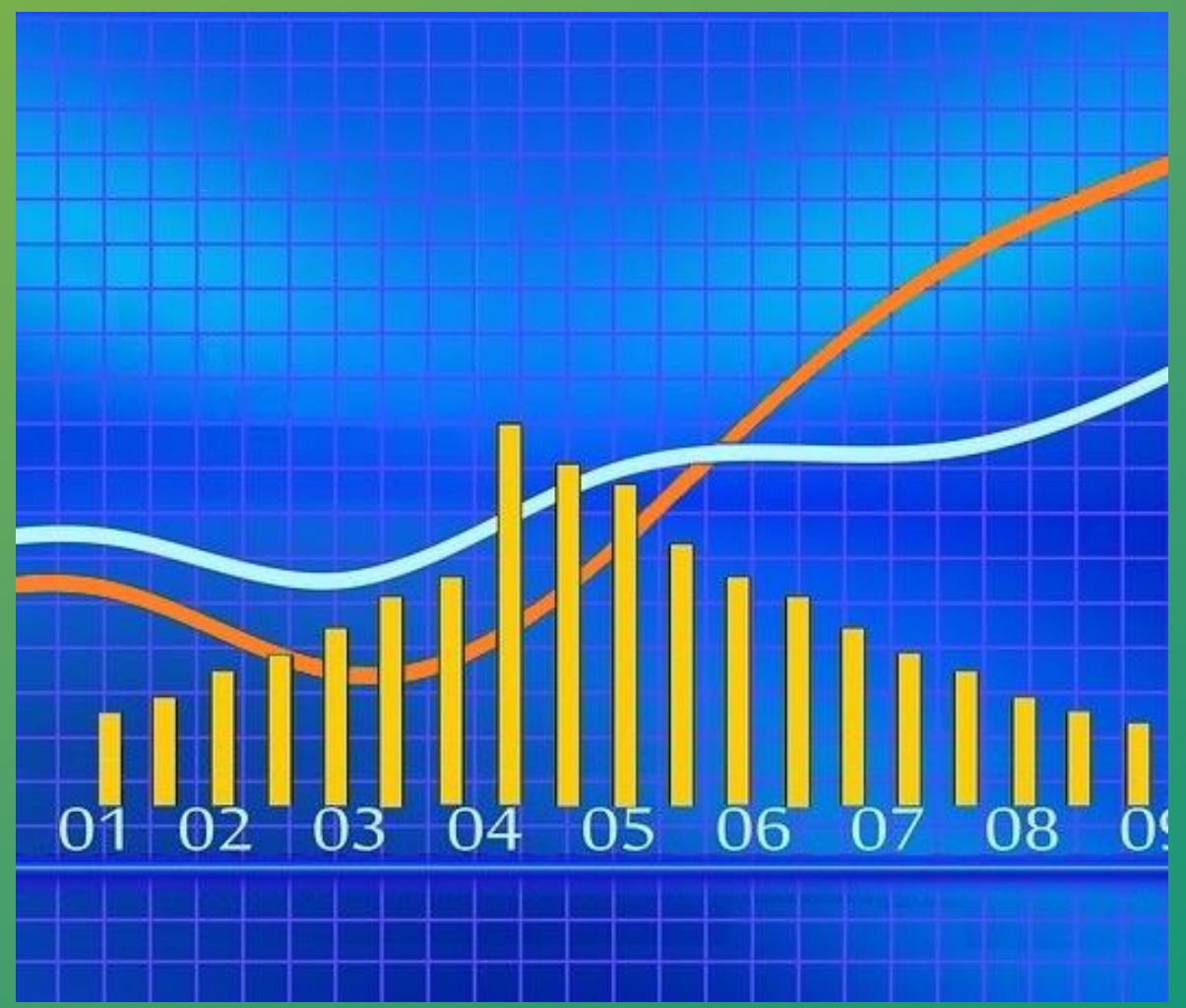
StabilityPlus™

A Versatile Stability Analysis Software



By
Biostat Plus, LLC

4/9/2021



Highlights

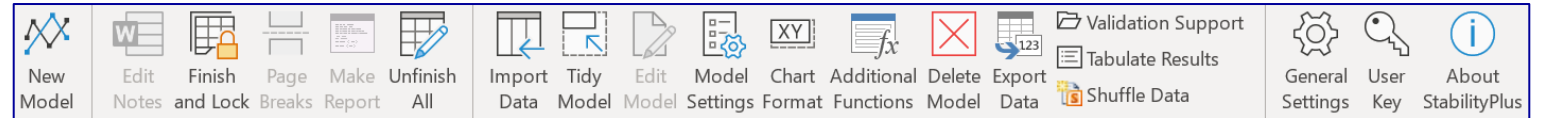
- ICH Q1E compliant stability analysis
- Easy ribbon tab user interface
- Quick, reliable, productivity enhancing tool
- Calculates ICH shelf-life estimates
- Versatile tool for stability analysis plus related functions
- Non-linear regression models
- Secure, integrity checked auto report generator
- Verified calculations using JMP, R, Minitab
- Tools for validation by end users

ICH Q1E analysis

- Common Slope, Separate Slopes, Common Line models
 - p-Values for pooling slopes, intercepts
- Calculates ICH shelf-life estimates
- Provides batch specific intercepts and slopes
 - Not easy in a general-purpose statistical software such as JMP
- Accommodates large number of lots and time points
- Customizable, submission ready plots exported to Word

Easy user interface

- Ribbon tab, dialogs
- Data import and export from Excel
- Text (<0.3, <LOQ, etc.) is grayed, not used in calculation
- Highlighted attention getters for slopes, shelf-life, p-values
- Specification decimals, etc. propagate to data, plot, report



Simulated down slope mean=100 procRSD=5 AssayRSD
down slope (arbitrary)

Month	Lot1	Lot2	Lot3	Lot4	Lot5	Lot6	Lot7	Lot8	Lot9
0	96.1	103.0	100.4	95.5	97.7	102.8	101.1	106.1	103.7
6		98.1		90.1		101.2		110.1	101.2
12	96.3	101.8	98.5	90.5	97.1		105.2	106.8	95.2
18	91.8		101.8	96.0	87.4	102.2		105.4	96.4
24	95.7	96.2	99.9		89.4	98.7	99.4	101.4	100.1
36	93.5	93.0	95.1	84.5	82.3	91.3		95.5	90.4
48	84.9	93.0	89.6	[115.6]		86.3	98.6		94.3
60	87.8	91.2	90.5	82.7	87.6	84.0		94.4	92.0
72	88.1	87.3	89.3	79.0	79.4		86.4		91.1
84	Any	text	is	ignored					
DoM	9May07	7Nov07	7May08	6Nov08	7May09	6Nov09	7May10	5Nov10	7May11

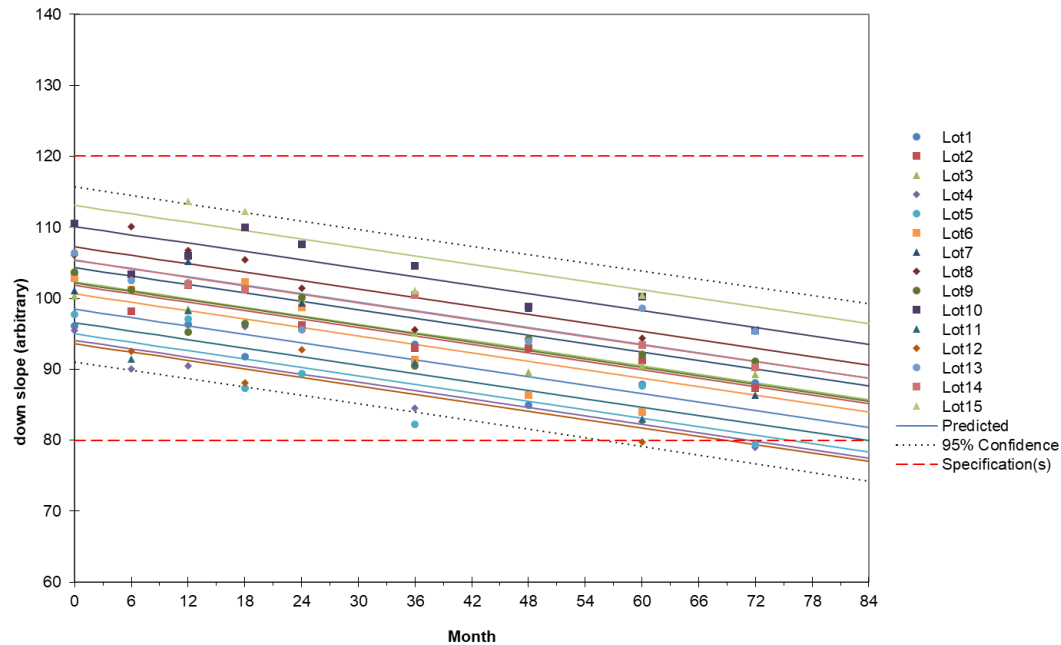
Model	Predicted Line	Estimated Life	Use	Slope(s) ²	Intercept(s)	N Lots
Common Slope	68.7 Month	55.6 Month	Y	-0.1979	93.6 to 113.1	15
Separate Slopes	62.1 Month	47.2 Month	I	-0.3477 to -0.1258	94.4 to 116.2	15
Common Line	112 Month	96.8 Month	N	-0.1975	102.1	15
Common Slope ⁴	87.5 Month	62.7 Month	Y	-1.757	96.4 to 116.3	15
Common Slope	48.8 Month	38.7 Month	Y	0.1944	93.1 to 110.5	15
Separate Slopes	52.2 Month	39 Month	I	0.0007 to 0.2587	92.9 to 111.1	15
Common Line	102.5 Month	89.4 Month	N	0.1911	100.4	15
Separate Slopes ⁴	63.1 Month	34.8 Month	I	0.186 to 2.231	91.2 to 110	15
Common Slope	671.2 Month	262.3 Month	N	-0.015	90.1 to 109.2	15
Separate Slopes	47.9 Month	28.6 Month	Y	-0.2987 to 0.0887	91.7 to 108.1	15
Common Line	9022.6 Mont	535.9 Month	N	-0.002205	99.89	15
Common Line ⁴	97812.5 Mor	2816.5 Mont	N	-0.06441	100.1	15

Versatile tool with many pluses

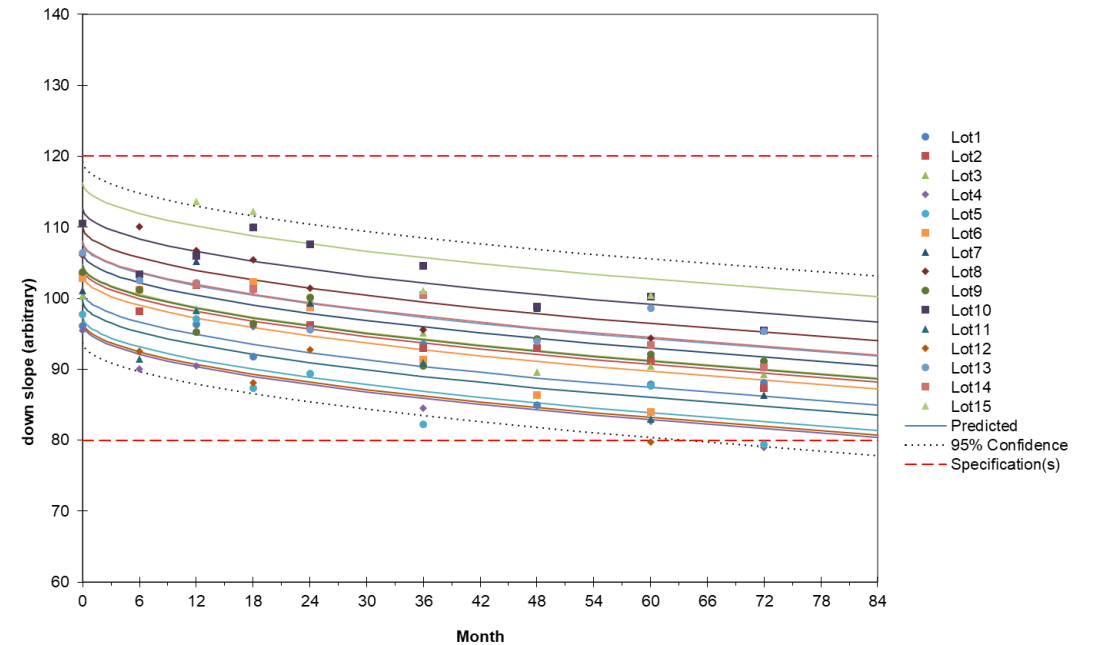
- Regression lines, 95% confidence and prediction limits
- Non-linear models for decreasing rate of change
- On-the-fly auto report generation
 - Customizable signature descriptions for e-signing or wet signing
- Release limits (to manage the risk of OOS in stability)
- Fitted, scatter or connected plots
- Diagnostic plots of residual and approximate assay date
- On-the-fly what-if analyses – just change data – no button click
- Flexible data input formats
- Functions to export plots to Word documents

Linear and non-linear regression plots

Simulated down slope mean=100 procRSD=5 AssayRSD=3 slope=-0.2

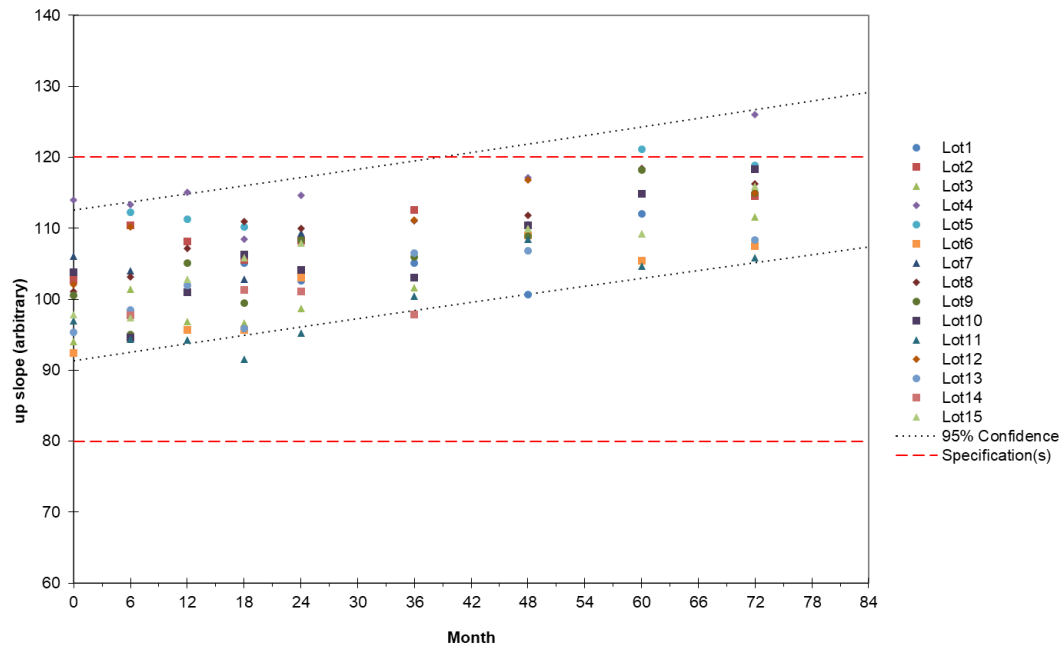


Simulated down slope mean=100 procRSD=5 AssayRSD=3 slope=-0.2



Scatter and connected plots

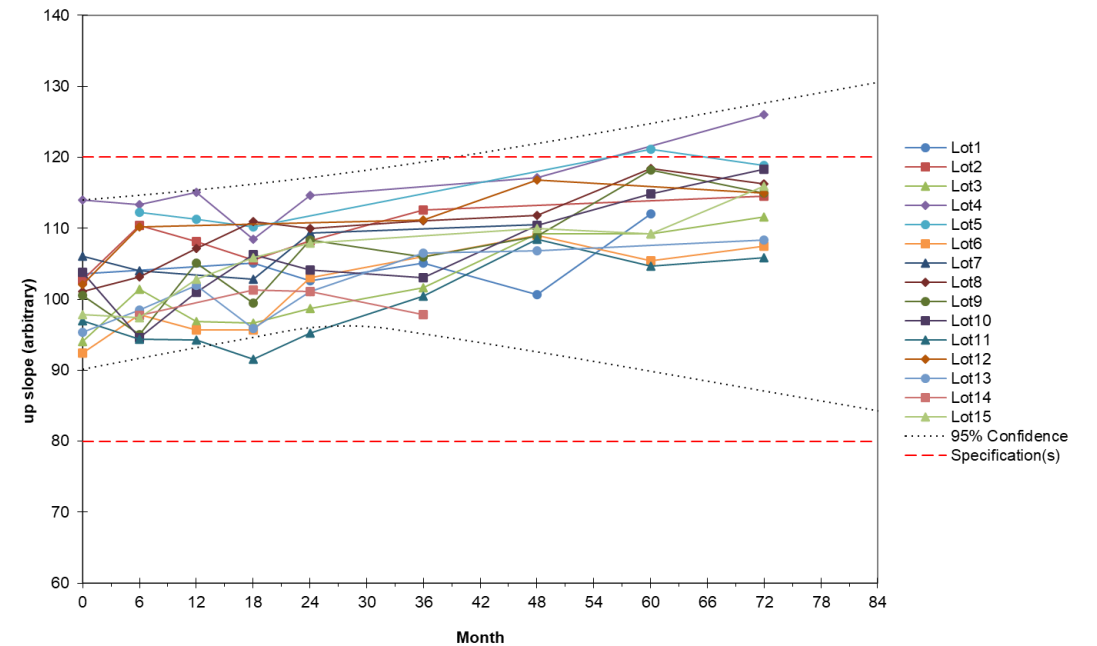
Simulated up slope mean=100 procRSD=5 AssayRSD=3 slope=0.2



Integrity check: <Chart passed>

Conforms to ICH, Q1E

Simulated up slope mean=100 procRSD=5 AssayRSD=3 slope=0.2

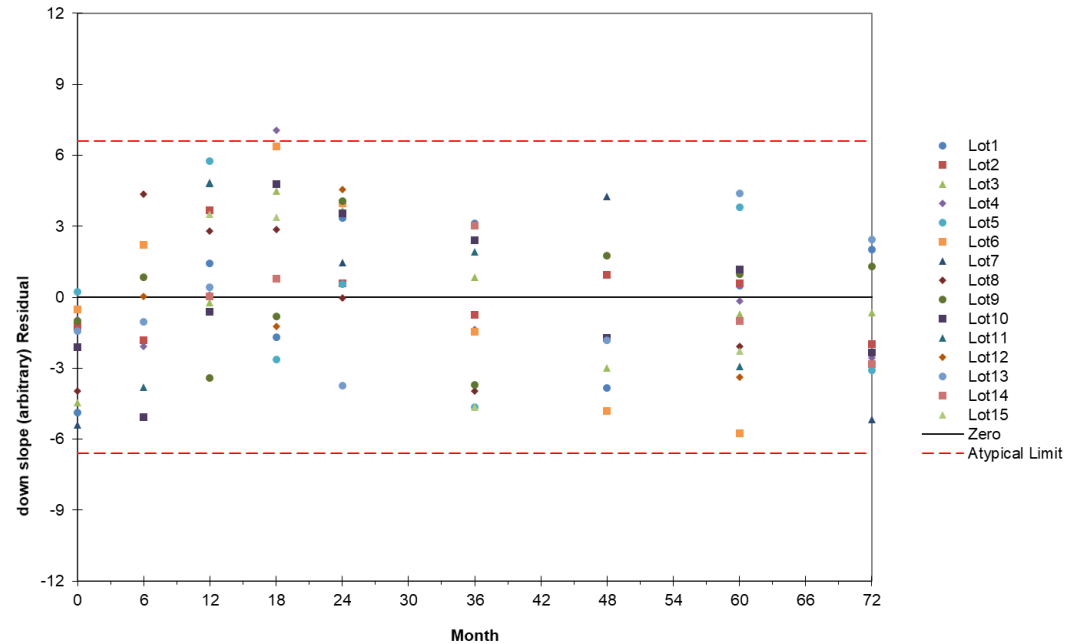


Integrity check: <Chart passed>

Poolable parameter(s)!

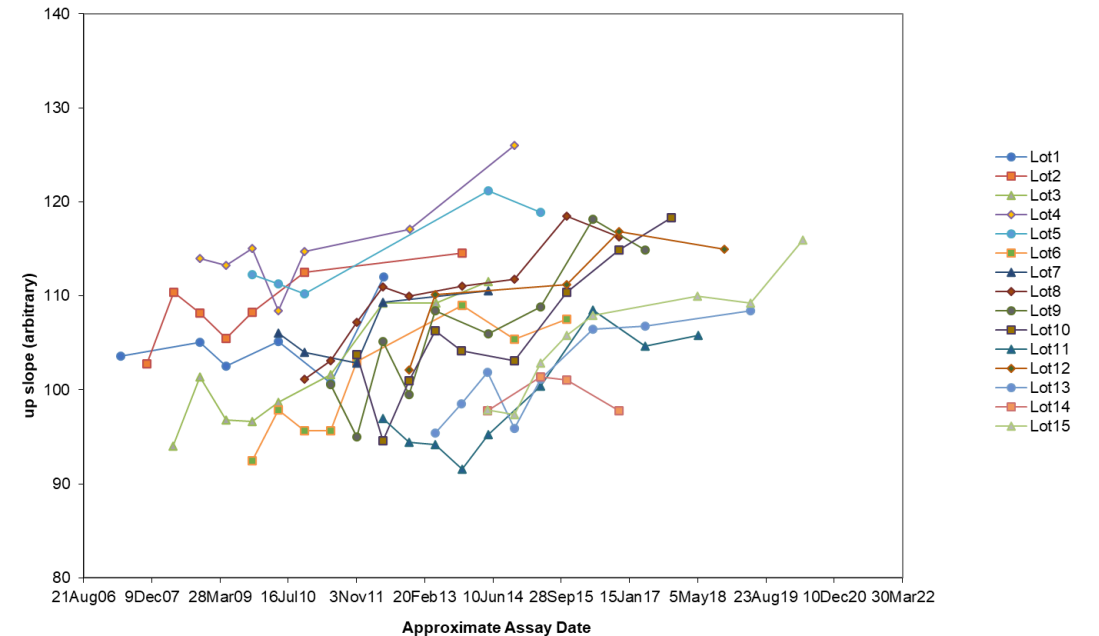
Residual, approx. assay date plots

Simulated down slope mean=100 procRSD=5 AssayRSD=3 slope=-0.2



Integrity check: <Chart passed>

Simulated up slope mean=100 procRSD=5 AssayRSD=3 slope=0.2



Integrity check: <Chart passed>

Secure, integrity checked reports

- Auto report generation
 - End user changes propagate to different parts of reports
 - Analysis recommendations customizable using Word
- Fool-proof, corruption-proof
 - Data validation checks
 - Functional integrity using circular redundancy check (CRC)
- PDF report
 - Embed analyst ID, analysis time, integrity check outcome
 - Customizable signature area
 - Report number option

Report Summary

Stability Analysis Summary

Description	Specification	Unit	Model	Predicted Line	Estimated Life	Use ¹	Slope(s) ²	Intercept(s)	N Lots	Data up to	Limiting Lot	Data up to	Poolable p-value? ³		Analysis Comment	
													Slopes	Intercepts		
Simulated down slope mean=100 procRSD=5% AssayRSD=3% slope=-0.2%/month	80	120	none	Common Slope	68.7 Month	55.6 Month	Y	-0.1979	93.6 to 113.1	15	72 Month	Lot12	60 Month	ICH (0.31)	No (0)	Conforms to ICH, Q1A,E
Simulated down slope mean=100 procRSD=5% AssayRSD=3% slope=-0.2%/month	80	120	none	Separate Slopes	62.1 Month	47.2 Month	I	-0.3477 to -0.1258	94.4 to 116.2	15	72 Month	Lot12	60 Month	ICH (0.31)	No (0)	Poolable parameter(s)!
Simulated down slope mean=100 procRSD=5% AssayRSD=3% slope=-0.2%/month	80	120	none	Common Line	112 Month	96.8 Month	N	-0.1975	102.1	15	72 Month	NA	NA	ICH (0.31)	No (0)	Not for NDA (ICH Q1A,E)
Simulated down slope mean=100 procRSD=5% AssayRSD=3% slope=-0.2%/month	80	120	none	Common Slope ⁴	87.5 Month	62.7 Month	Y	-1.757	96.4 to 116.3	15	72 Month	Lot12	60 Month	ICH (0.76)	No (0)	Conforms to ICH, Q1A,E
Simulated up slope mean=100 procRSD=5% AssayRSD=3% slope=0.2%/month	80	120	none	Common Slope	48.8 Month	38.7 Month	Y	0.1944	93.1 to 110.5	15	72 Month	Lot4	72 Month	ICH (0.46)	No (0)	Conforms to ICH, Q1A,E
Simulated up slope mean=100 procRSD=5% AssayRSD=3% slope=0.2%/month	80	120	none	Separate Slopes	52.2 Month	39 Month	I	0.0007 to 0.2587	92.9 to 111.1	15	72 Month	Lot4	72 Month	ICH (0.46)	No (0)	Poolable parameter(s)!
Simulated up slope mean=100 procRSD=5% AssayRSD=3% slope=0.2%/month	80	120	none	Separate Slopes	52.2 Month	39 Month	I	0.0007 to 0.2587	92.9 to 111.1	15	72 Month	Lot4	72 Month	ICH (0.46)	No (0)	Poolable parameter(s)!
Simulated up slope mean=100 procRSD=5% AssayRSD=3% slope=0.2%/month	80	120	none	Common Line	102.5 Month	89.4 Month	N	0.1911	100.4	15	72 Month	NA	NA	ICH (0.46)	No (0)	Not for NDA (ICH Q1A,E)
Simulated up slope mean=100 procRSD=5% AssayRSD=3% slope=0.2%/month	80	120	none	Separate Slopes ⁴	63.1 Month	34.8 Month	I	0.186 to 2.231	91.2 to 110	15	72 Month	Lot4	72 Month	ICH (0.5)	No (0)	Poolable parameter(s)!
Simulated no slope mean=100 procRSD=5% AssayRSD=3% slope=0%/month	80	120	none	Common Slope	671.2 Month	262.3 Month	N	-0.015	90.1 to 109.2	15	72 Month	Lot8	24 Month	No (0.03)	No (0)	Not for NDA (ICH Q1A,E)
Simulated no slope mean=100 procRSD=5% AssayRSD=3% slope=0%/month	80	120	none	Separate Slopes	47.9 Month	28.6 Month	Y	-0.2987 to 0.0887	91.7 to 108.1	15	72 Month	Lot8	24 Month	No (0.03)	No (0)	Poolable parameter(s)!
Simulated no slope mean=100 procRSD=5% AssayRSD=3% slope=0%/month	80	120	none	Common Line	9022.6 Month	535.9 Month	N	-0.002205	99.89	15	72 Month	NA	NA	No (0.03)	No (0)	Not for NDA (ICH Q1A,E)
Simulated no slope mean=100 procRSD=5% AssayRSD=3% slope=0%/month	80	120	none	Common Line ⁴	97812.5 Month	2816.5 Month	N	-0.06441	100.1	15	72 Month	NA	NA	NS (0.09)	No (0)	Not for NDA (ICH Q1A,E)

¹ Model recommended for use: Y - Yes; N - No; M - May be acceptable; I - For information

² Any statistically significant common slope (from a common slope or common line model) is highlighted in red

³ ICH: Poolable per ICH guidelines Q1A,E (p>0.25), NS: Not statistically significant (p≥0.05), No: Not poolable

⁴ These models use $\sqrt{\text{time}}$ as regressor and slopes are with respect to $\sqrt{\text{time}}$

Unless specified, p-value refers to the poolability of batch/lot slopes. Abbreviations: CS - Common Slope; SS - Separate Slopes; CL - Common Line

Notes

Down Slope

ICH guideline of $p > 0.25$ for NDA for pooling batch specific slopes to a common slope is met. Observed p-value = 0.31. Common slope (-0.20) is statistically significant. Estimated life with CS model is 56 months.

The limiting lot Lot12 has 60 months of data. Unrounded result 79.8 for this batch at 60 months rounds to 80 at the specification precision and meets the lower specification limit of 80.

CS model with respect to time ($r^2=0.8645$, s.e. residuals = 3.02) fits the data better than the CS model against square root time ($r^2=0.8360$, s.e. residuals = 3.32).

Analysis Performed by

Date:

Analysis Reviewed by

Date:

Data Reviewed by

Date:



Built-in and packaged validation tools

- Export function to summarize results in a spreadsheet
- For easy comparison using R, JMP, Minitab, etc.
- Steps to verify calculations using R, JMP and Minitab
- Example (simulated) stability data
- Simulated data generator R code
- Example stability analysis reports
- Documented comparisons using R, JMP and Minitab
- Stability calculation and comparison R code

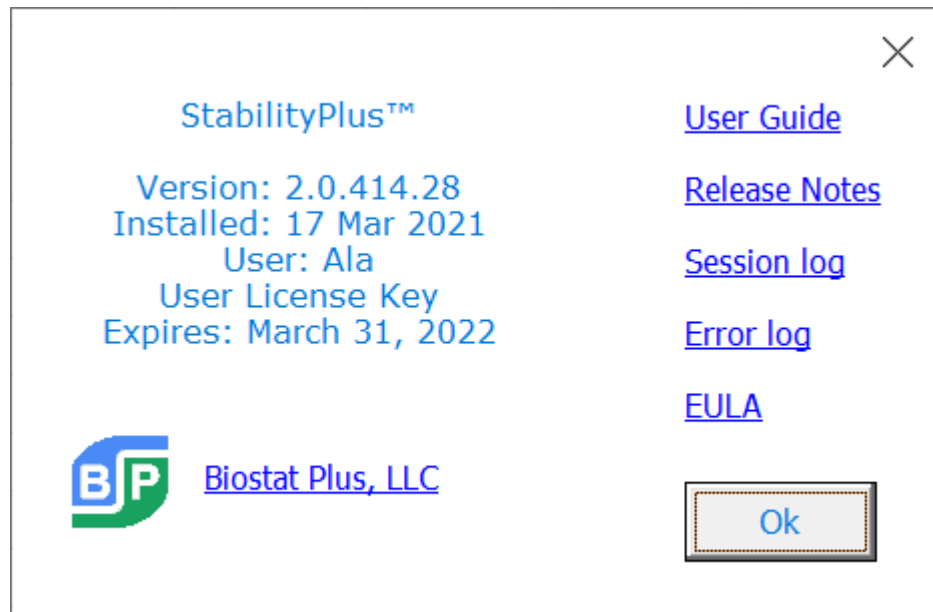
Results using StabilityPlus and R

	Results
StabilityPlus Version	2.0.414
Analysis Workbook	Analysis by StabilityPlus.xlsx
Analysis name	down slope CS Data
attribute	Simulated down slope mean=100
n lots	15
n times	9
max time	72 Month
n points	100
model type	Common Slope
linearize with sqrt(time)	FALSE
p-diff batch intercepts?	4.57E-22
p-diff batch slopes?	0.30831
intercept	93.6 to 113.1
slope	-0.1979
p-slope	9.44E-26
std err slope	0.01306
std err residuals	3.01792
deg freedom residuals	84
r-square	0.8645
adj. r-square	0.8403
Lot Lot12 Pred value at 68.75312	80
Lot Lot12 Conf limit at 55.68655	80

	value
R version	R version 3.6.3 (2020-02-29)
file name	Simulated data.xlsx
sheet name	down slope
attribute	Simulated Stability Data mean=100
n lots	15
n times	9
max time	72
n points	100
model type	Common Slope
linearize with sqrt(time)	FALSE
p-diff batch intercepts?	4.57E-22
p-diff batch slopes?	0.30831
intercept	93.61 to 113.1
slope	-0.1979
p-slope	9.44E-26
std err Slope	0.01306
std err residuals	3.017920
deg freedom residuals	84
r-square	0.8645
adj. r-square	0.8403
lot Lot12 pred value at 68.75312	80
lot Lot12 lower conf limit at 55.68655	80

License details

- Individual license key
- For windows username/domain name combination



<https://biostatplus.com>