

Statistical analysis of stability data

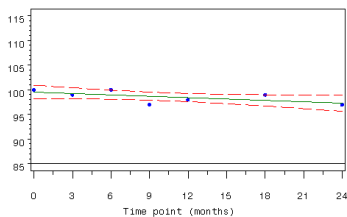


The simplified story

- Look at the drug product for a long period of time
- Measure the level of an interesting parameter at several time points
- See if it changes over time

Simple linear model

- Y = the measured parameter (e.g. %assay, pH)
- T = time (typically measure in months)
- Model: $Y = \beta_0 + \beta_1 \cdot T + \varepsilon$



Analysis of more than one batch

- Usually, data from one batch is not enough - in most cases we need 3 batches
- We can analyze each batch separately, but then we must consider the worst case scenario
- Also, the variability in a single batch is large compared to the variability in a larger sample

The complicated story

- Receive stability data from a few batches
- Determine if the data from the various batches can be pooled together
- If yes, analyze the pooled data

Model for testing poolability

- Y = the measured parameter (e.g. %assay, pH)
- T = time (typically measure in months)
- B = the batch
- $B \cdot T$ = batch and time interaction
- Model: $Y = \beta_0 + \beta_1 \cdot T + \beta_2 \cdot B + \beta_3 \cdot T \cdot B + \varepsilon$

How to test for poolability

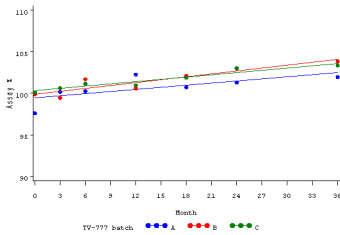
- If interaction term is significant, data cannot be pooled
- If interaction term is not significant...
 - If batch is significant, then it must remain in the model
 - Otherwise, data can be pooled completely

Each of these tests should be conducted using a significance level of 0.25 to compensate for the expected low power of the design due to the relatively limited sample size in a typical formal stability study

Specification checking

- For an attribute known to **decrease** with time, the **lower one-sided 95 percent confidence limit** should be compared to the acceptance criterion
- For an attribute known to **increase** with time, the **upper one-sided 95 percent confidence limit** should be compared to the acceptance criterion
- For an attribute that can **either increase or decrease**, or whose **direction of change is not known**, **two-sided 95 percent confidence limits** should be calculated and compared to the upper and lower acceptance criteria

Example 1 - poolability test



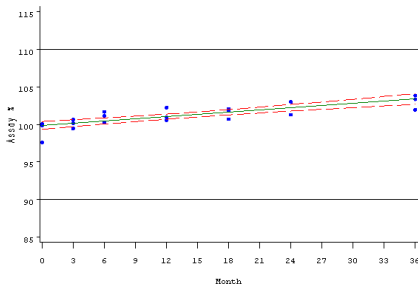
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	1.07108035	0.53554017	0.77	0.4825
Month	1	28.12979809	28.12979809	48.20	<.0001
Month*Batch	2	0.56687516	0.28343758	0.41	0.6740

Example 1 - Analysis

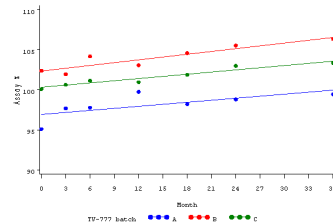
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	28.12979809	28.12979809	35.27	<.0001

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	99.86365365	0.30327273	329.29	<.0001
Month	0.09757444	0.01643002	5.94	<.0001

Example 1 - Specification checking



Example 2 - poolability test



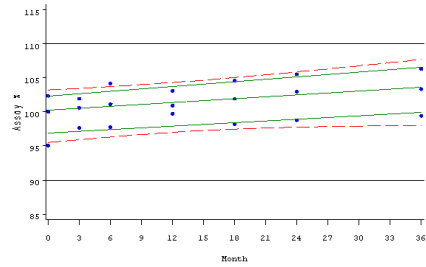
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	43.8866227	21.7923113	31.15	<.0001
Month	1	28.12979809	28.12979809	48.20	<.0001
Month*Batch	2	0.56687516	0.28343758	0.41	0.6740

Example 2 - Analysis

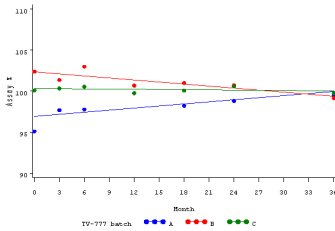
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	123.1086280	61.5543140	94.60	<.0001
Month	1	28.1297981	28.1297981	43.23	<.0001

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	100.2092510	0.37014556	270.73	<.0001
Batch A	-3.4686325	0.43117638	-8.04	<.0001
Batch B	2.4318404	0.43117638	5.64	<.0001
Batch C	0.0000000	.	.	.
Month	0.0975744	0.01484027	6.57	<.0001

Example 2 - Specification checking



Example 3 - poolability test



Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	43.68866227	21.79283113	31.15	<.0001
Month	1	0.01738277	0.01738277	0.02	0.8769
Month*Batch	2	13.87330090	6.93665045	9.91	0.0018

Example 3 - Analysis

TV-777 batch-A					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	6.9813149	6.9813149	4.75	0.0311

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	96.9292838	0.71317814	136.91	<.0001
Month	0.08421718	0.03063679	2.78	0.0111

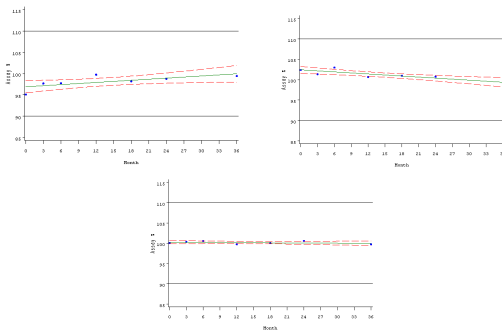
TV-777 batch-B					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	6.84004023	6.84004023	13.69	0.0149

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	102.3711378	0.41082030	246.19	<.0001
Month	-0.0833379	0.02252788	-3.70	0.0149

TV-777 batch-C					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	0.06651191	0.06651191	0.51	0.4979

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	106.2902948	0.21123473	474.70	<.0001
Month	-0.0010599	0.01144880	-0.71	0.4979

Example 2 - Specification checking



Guidelines and references

- EP Chapter 5.3
- USPC General Chapter <111>
- Statistics in the Pharmaceutical Industry: Ch. 3