Stability and shelf life estimation

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Regulatory background

- 6 guidelines (Q1A-Q1F) cover all aspects of stability and shelf life estimation
- Two of them are relevant for statisticians
  - Q1A - Stability Testing of New Drug Substances and Products
  - Q1E - Evaluation of Stability Data

What is shelf life?

Labeled shelf-life … provides the consumer the confidence that the drug product will retain its identity, strength, quality, and purity throughout the expiration period of the drug product

Chow, 2007

The maximum time at which a stability limiting characteristic stays within acceptance criteria

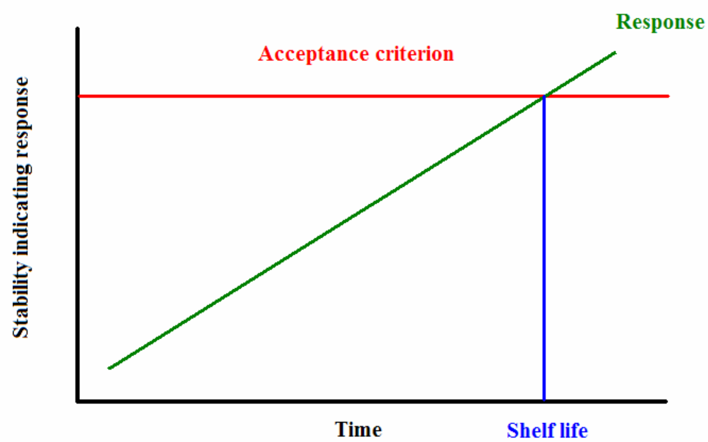
ICH Q1A

Shelf life – statistical definition

The maximum time at which the true mean response of a stability limiting characteristic crosses the acceptance criterion

ICH Q1A

The statistical paradigm



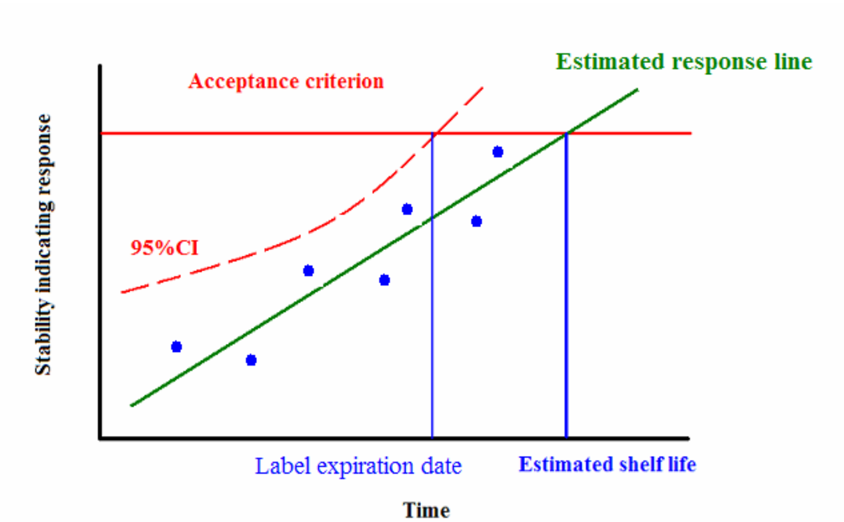
The statistical challenge

- The true mean response is not known
- But it can be estimated
- How?

The simple experimental design

- Put the product on the shelf
- Measure its stability indicating characteristics once in a while
- Estimate the response line, e.g. using linear regression

Extended paradigm



What should be modeled?

- Individual tablets (syringes/etc.)?
- Composite sample of several tablets?
- Packaged unit (bottle or blister pack)?
- Batches?
  - Special stability batches or all future batches?

Design considerations

- Effect of environmental factors – temperature, humidity, etc.
- Effect of packaging type – bottles, blisters, etc.
- Effect of dose – usually can be combined into one study, if formulations are similar

Storage conditions

- Storage conditions reflect the environmental factors
- Three levels
  - Recommended storage conditions (e.g. room temperature)
  - Intermediate storage conditions
  - Accelerated storage conditions

Recommended conditions

- E.g. room temperature: 25ºC/60%RH
- Long term testing – up to the desired shelf life, and maybe beyond that
- Test frequency
  - 1st year – every three months
  - 2nd year – every six months
  - Thereafter - annually

Accelerated conditions

- E.g. $40^{o}C/75\%RH$
- Designed to increase the rate of chemical degradation or physical change
- Test duration – 6 months
- At least 3 time points are required
- Stability in 6 months of accelerated storage conditions supports 2 years of shelf life in recommended storage conditions

Accelerated conditions significant change

- 5% change in assay value from its initial value
- Any degradation product exceeding its acceptance criterion
- Failure to meet acceptance criteria for stability indicating characteristics

Intermediate conditions

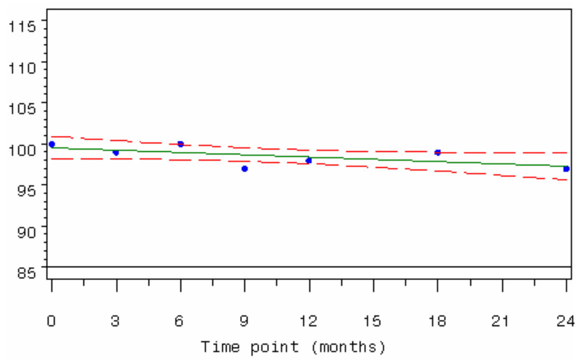
- E.g. 30°C/65%RH
- Triggered when a significant change is observed in accelerated conditions
- Testing time points: time zero, and from point of significant change onward

Statistical evaluation

- Not always needed – sometimes it suffices just to present the graphs
- Needed when
  - The company wishes to pool data from several batches
  - The company wishes to extrapolate the shel life beyond the test period
  - Bad things happen…

Simple linear model

- Y_T = the measured parameter at time T
- T = time (typically measured in months)
- Model: $Y_T = \beta_0 + \beta_1 \cdot T + \varepsilon$



Design issues

- What would be the “sample size”?
- Are statistical assumptions valid?
  - Distribution
  - Independence
  - Homogeneity

ICH methodology

- Minimum of three batches
- Batches are considered as fixed effects
- Data from batches can be pooled if there are no significant differences between batches
- Shelf life is determined by crossing point of acceptance criterion and 95% confidence interval for the mean

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

Multiple batches

- Each batch can be analyzed separately – but then the shelf life is determined by the "worst case"
- Or we can analyze data from all batches in one model, controlling for the batch as a covariate

Model for multiple batches

- Y_{TB} = the measured parameter from batch B at time T
- T = time (typically measure in months)
- B = the batch
- B*T = batch and time interaction
- Model:

$$Y_{TB} = \beta_0 + \beta_1 \cdot T + \beta_2 \cdot B + \beta_3 \cdot T \cdot B + \varepsilon$$

Four models

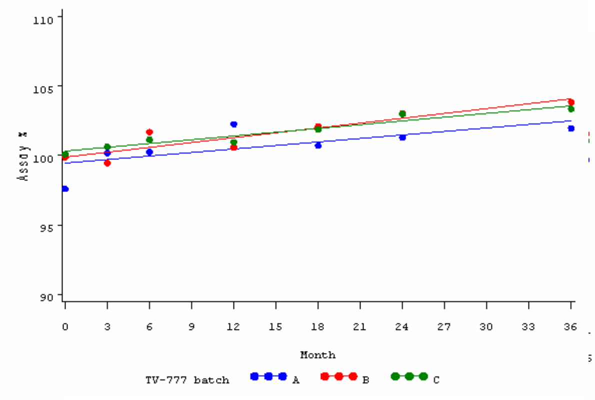
1. Unequal intercepts and slopes ($\beta_2 \neq 0$ and $\beta_3 \neq 0$) => Analyze each batch separately
2. Common intercept, unequal slopes ($\beta_2 = 0$ and $\beta_3 \neq 0$) – not allowed by ICH
3. Unequal intercepts, common slope ($\beta_2 \neq 0$ and $\beta_3 = 0$)
4. Common intercept and slope ($\beta_2 = \beta_3 = 0$) – pooled analysis

Model selection procedure

1. Test H_0: $\beta_3 = 0$. If rejected – analyzed each batch separately
2. If H_0: $\beta_3 = 0$ is not rejected, then test H_0: $\beta_2 = 0$
   a) If rejected, use parallel slope model
   b) Otherwise, all batches can be pooled

These tests can be performed at a significance level of $\alpha = 0.25$

Example 1 - poolability test



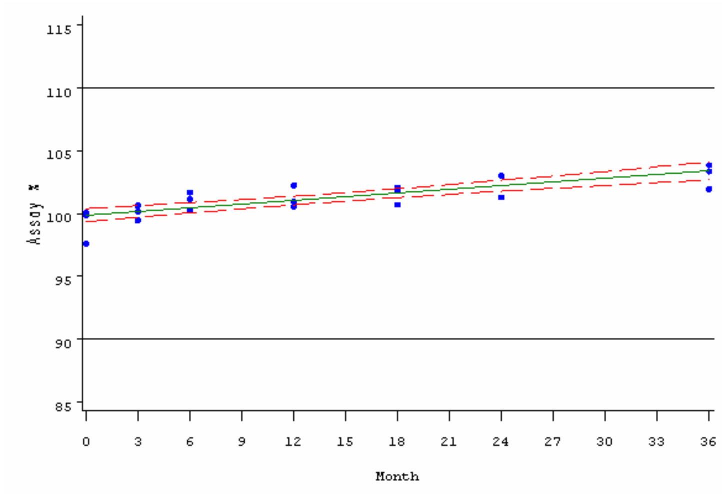
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	1.07108035	0.53554017	0.77	0.4825
Month	1	28.12979809	28.12979809	40.20	<.0001
Month*Batch	2	0.56687516	0.28343758	0.41	0.6740

Example 1 - Analysis

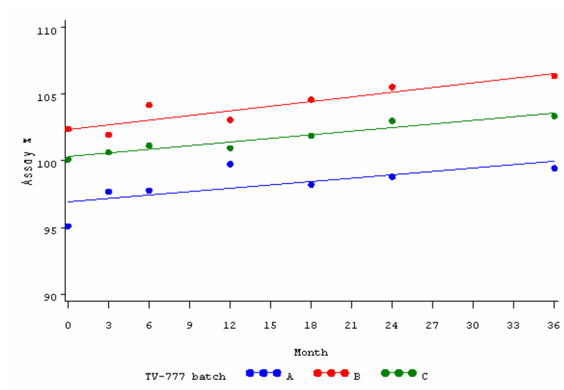
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	28.12979809	28.12979809	35.27	<.0001

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



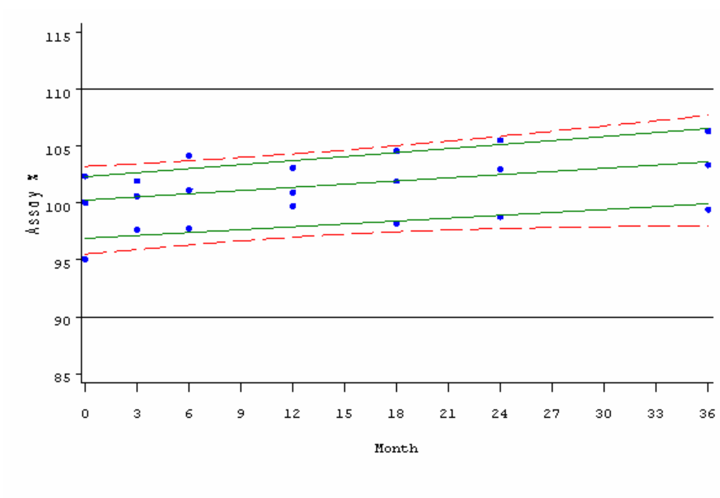
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	43.58566227	21.79283113	31.15	<.0001
Month	1	28.12979809	28.12979809	40.20	<.0001
Month*Batch	2	0.56687516	0.28343758	0.41	0.6740

Example 2 - Analysis

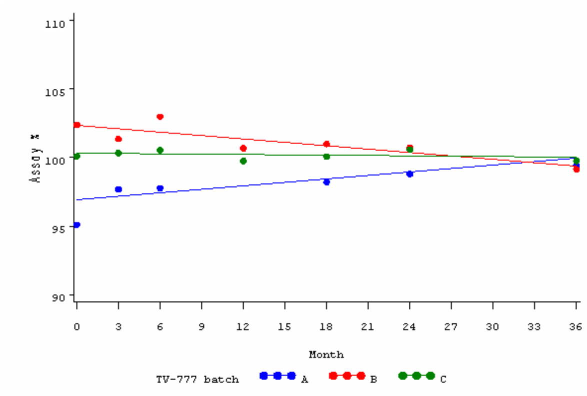
Source	DF	Type III SS	Mean Square	F Value	Pr > F
Batch	2	123.1086280	61.5543140	94.60	<.0001
Month	1	28.1297981	28.1297981	43.23	<.0001

Parameter	Estimate		Standard Error	t Value	Pr > |t|
Intercept	100.2092510	B	0.37014556	270.73	<.0001
Batch A	-3.4686325	B	0.43117638	-8.04	<.0001
Batch B	2.4318404	B	0.43117638	5.64	<.0001
Batch C	0.0000000	B	.	.	.
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	43.58566227	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	6.98513149	6.98513149	4.75	0.0811

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	96.92952835	0.71317514	135.91	<.0001
Month	0.08421718	0.03863679	2.18	0.0811

TV-777 batch=B

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	6.84004028	6.84004028	13.69	0.0140

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	102.3711378	0.41582830	246.19	<.0001
Month	-0.08333379	0.02252780	-3.70	0.0140

TV-777 batch=C

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Month	1	0.06551191	0.06551191	0.51	0.5079

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	100.2902948	0.21123473	474.78	<.0001
Month	-0.0081559	0.01144380	-0.71	0.5079

Example 3 - Specification checking