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Comparability of stability data

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Scope

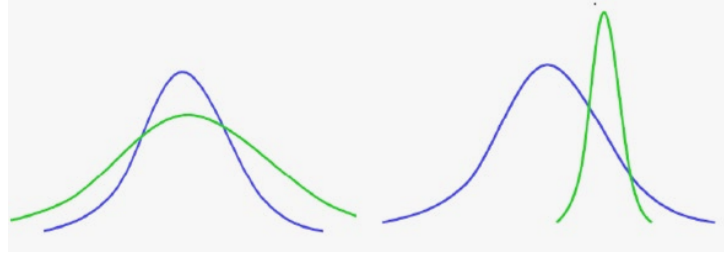
- Comparison of DP or DS batches pre- and post-manufacturing change
 - Demonstrate that a change does not adversely affect product's identity, strength, quality, purity, or potency
- Technology transfer to a new production site, filling line etc
 - Ensure continuity in product quality and regulatory compliance
- Scale down model is representative of the full scale process
 - Verify that models on smaller scale accurately reflect performance and outcomes of commercial-scale process
- Qualification/ impact of reagent, equipment (Future vs current)
 - Ensure that changes do not compromise product quality or process performance
- Equivalence between a bio similar candidate and a reference DP
 - May have particular constraints (e.g. different age of batches)

Situations

- Comparability of Release

Difference of means

⇒ Equivalence approaches



Difference in individual values

⇒ Interval approaches

*Figures 2 and 3 from EMA reflection paper

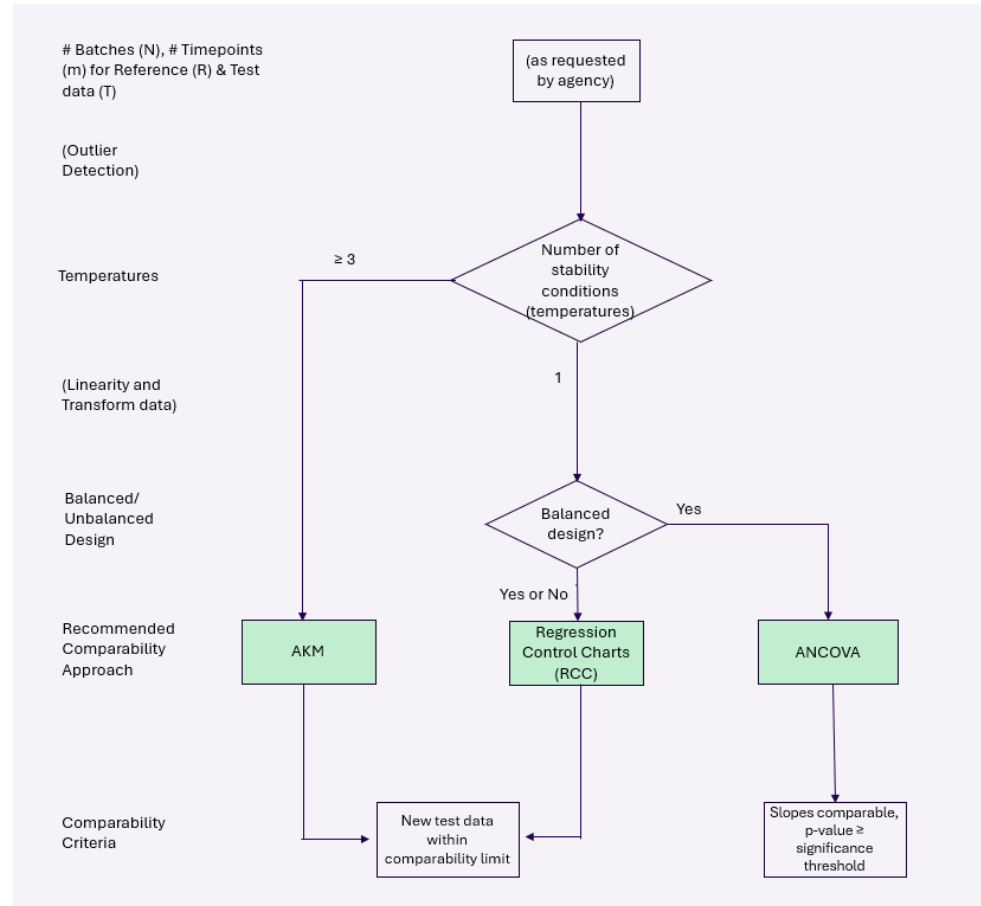
- Comparability of stability

- Ancova with add. Factor

- Advanced kinetic modelling (AKTS)

- Regression control chart

Decision tree



Analysis of Covariance

- ANCOVA according to ICH with additional factor (with i the batch and j the process):

$$Y_{ij} = batch_i + process_j + time + batch_i * time + process_j * time + \varepsilon_{ij}$$

$$Y_{ij} = \alpha_{ij} + \beta_{ij} * time + \varepsilon_{ij}$$

- Stepwise reduction of model

- Poolability of slopes within each process $\Rightarrow \hat{Y}_{ij} = \alpha_{ij} + \beta_{.j} * time$

- Poolability of slopes within and between processes $\Rightarrow \hat{Y}_{ij} = \alpha_{ij} + \beta_{..} * time$

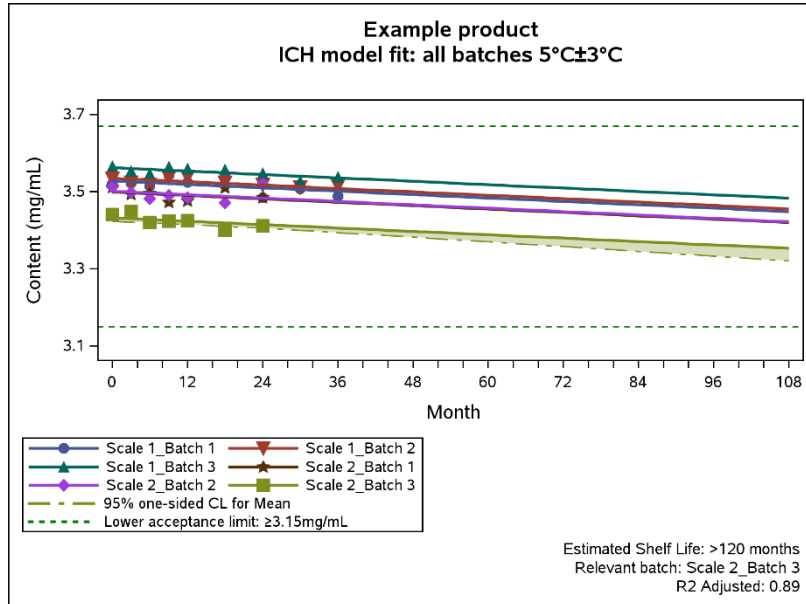
- Only for information:

- Poolability of intercepts within each process $\Rightarrow \hat{Y}_{ij} = \alpha_{.j} + \beta_{..} * time$

- Poolability of intercepts within and between processes $\Rightarrow \hat{Y}_{ij} = \alpha_{..} + \beta_{..} * time$

Analysis of Covariance

- Example process upscale



Effect	Hypothesis	Num DF	Den DF	F Value	Pr > F	Result
month*Batch(factor)	H0: Equality of slopes within each factor level	4	36	0.92	0.4632	H0 <u>accepted</u>
month*factor	H0: Equality of slopes between factor levels	1	40	0.03	0.8710	H0 <u>accepted</u>
Batch(factor)	H0: Equality of intercepts within each factor levels	4	41	37.25	<.0001	H0 <u>rejected</u>
month	H0: Pooled slope is equal to 0	1	41	14.68	0.0004	H0 <u>rejected</u>

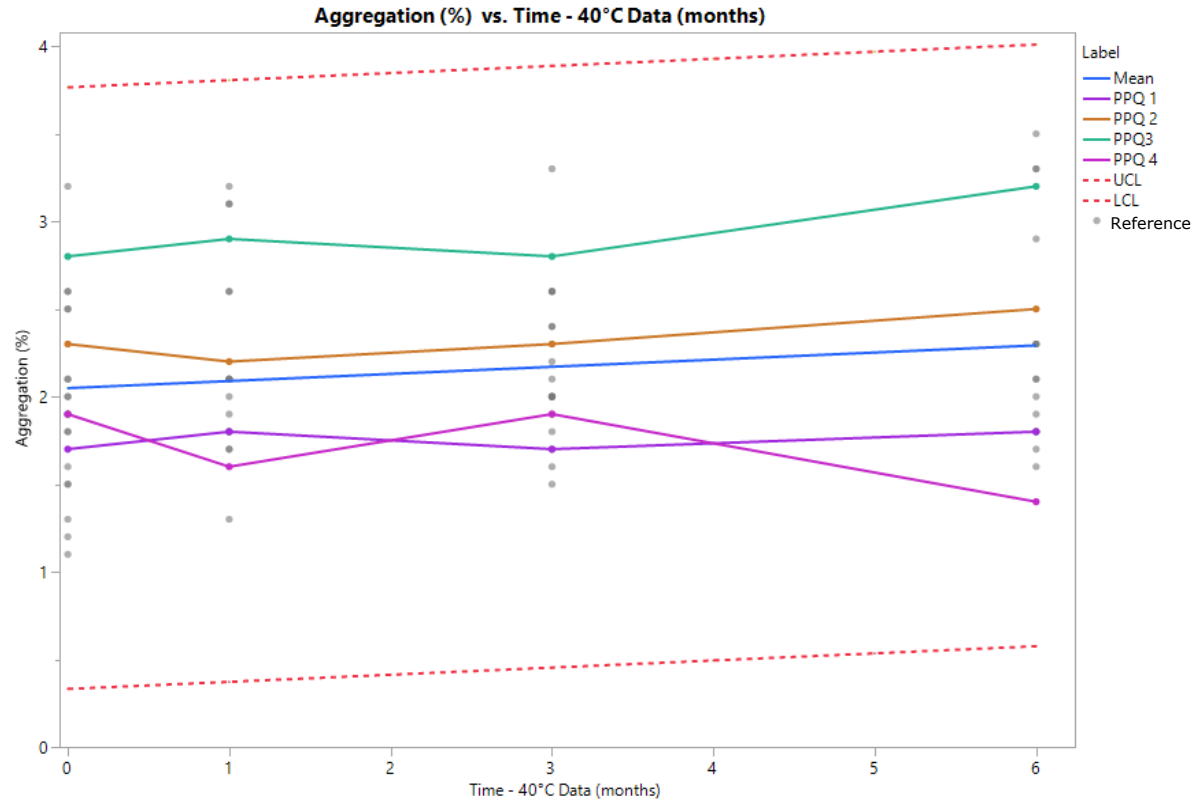
Scale	Batch	Estimated intercept	Estimated slope	Specification limit	Predicted value* at 30 months (95% OLCL)
Scale 1	Batch 1	3.5276	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.51mg/mL (3.50mg/mL)
	Batch 2	3.5347	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.51mg/mL (3.50mg/mL)
	Batch 3	3.5620	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.54mg/mL (3.53mg/mL)
Scale 2	Batch 1	3.4990	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.48mg/mL (3.47mg/mL)
	Batch 2	3.5011	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.48mg/mL (3.47mg/mL)
	Batch 3	3.4323	-73E-5 (p=0.0004)	≥ 3.15 mg/mL	3.41mg/mL (3.40mg/mL)

Regression Control Chart

- Equivalent to Statistical Process Control
 - Simple linear regression from reference batches $\bar{y}_l = \beta_0 + \beta_1 * x$
 - With upper and lower control limits $\bar{y}_l \pm k * \sigma_{error}$
 - $\bar{y}_l$ predicted y described by linear regression with intercept β_0 , slope β_1 and timepoint x
 - The standard deviation σ_{error}
 - k=3 to represent a 99.73% confidence interval
- Timepoints of test batches have to fall within the comparability interval of $\pm 3 \sigma$

Regression Control Chart

- Example technology transfer (new site)



Advanced kinetic modelling

- One-step and two-step Arrhenius-based differential equations

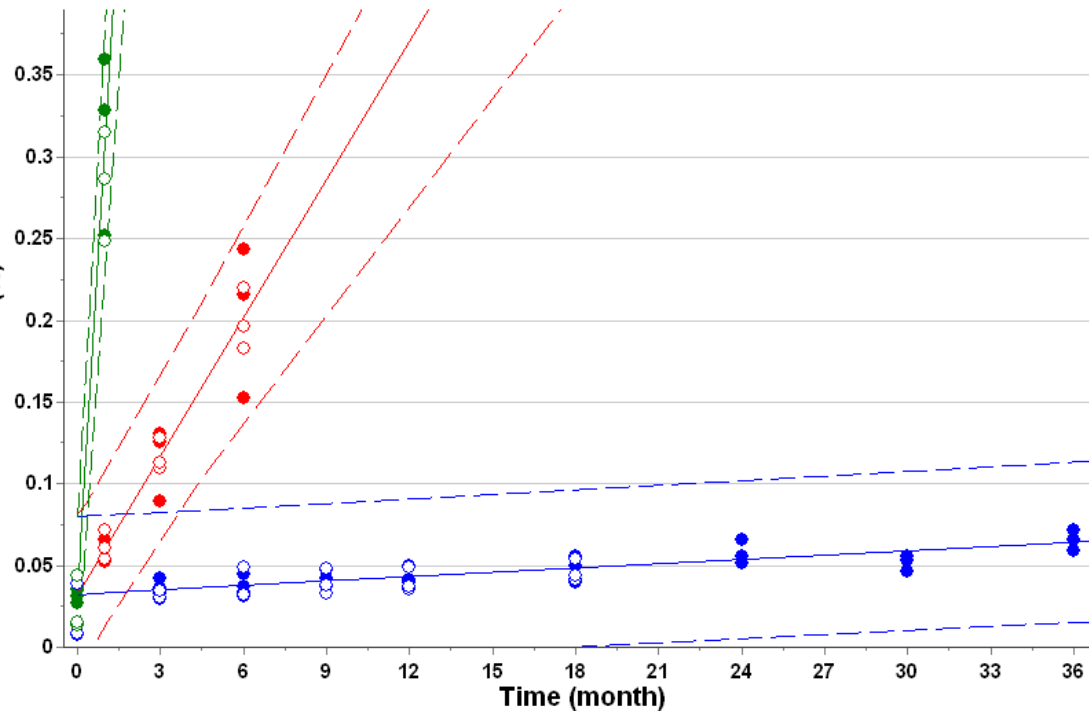
$$\frac{d\alpha}{dt} = A \exp\left(-\frac{E_{\alpha}}{RT}\right) (1 - \alpha)^n \alpha^m$$

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{\alpha_1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{\alpha_2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$

- reaction progress α
 - pre-exponential factor A
 - activation energy E
 - reaction order n
 - dimensionless autocatalytic-behaviour parameter m
- Model building from reference batches, including 99% prediction interval
 - For comparability purpose, simpler models (“describing well observed reference data”) can be reasonably used
 - Measurements from test batches need to be in the interval

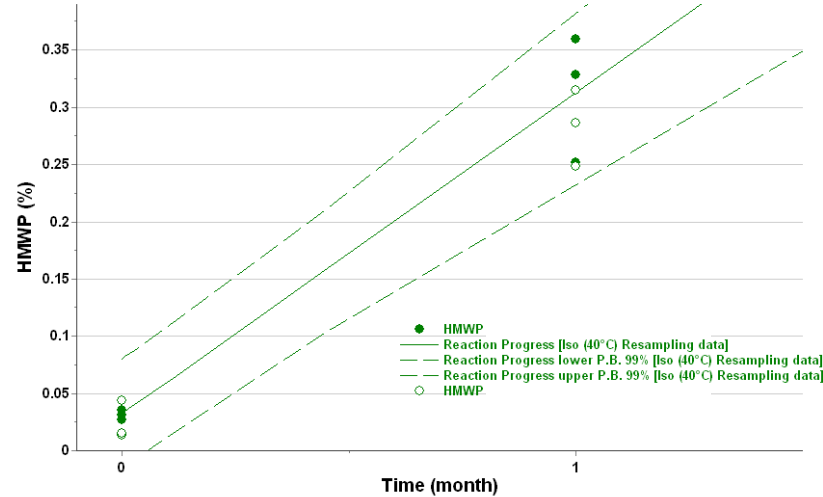
Advanced kinetic modelling

- Example technology transfer (line transfer)
- Model fit from stability batches from reference line (lines and filled circles)
 - Long-term, accelerated and stress condition
 - Linear model chosen for simplicity
- Stability batches from new production line (empty circles) within the 99% Prediction band (dashed lines)

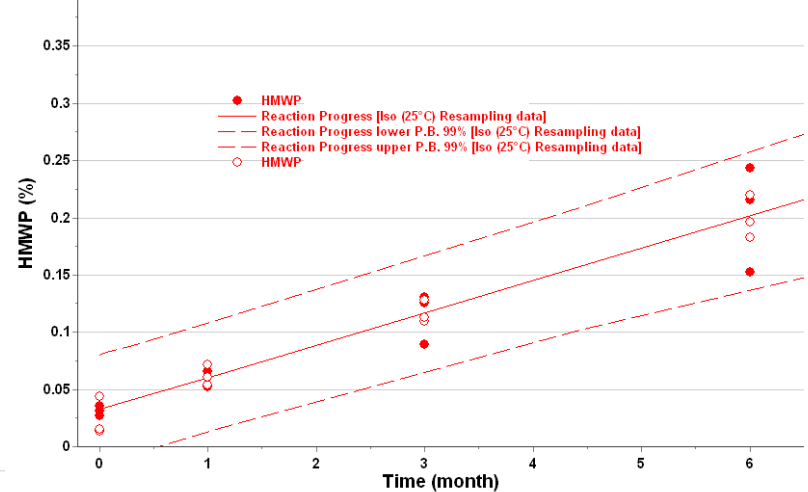


$$\frac{da}{dt} = \exp(20.01) * \exp(-1.188E+5/8.314/T) * (1-a)^0 * a^0; \alpha_{Aging} = 1E-10$$

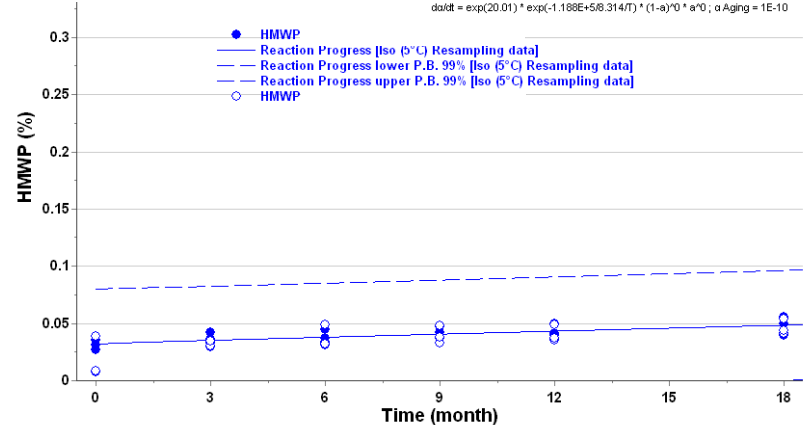
Advanced kinetic modelling



$\text{data}(\text{t}) = \exp(20.01) * \exp(-1.188E+5/8.314/T) * (1-a)^0 * a^0 ; a \text{ Aging} = 1E-10$

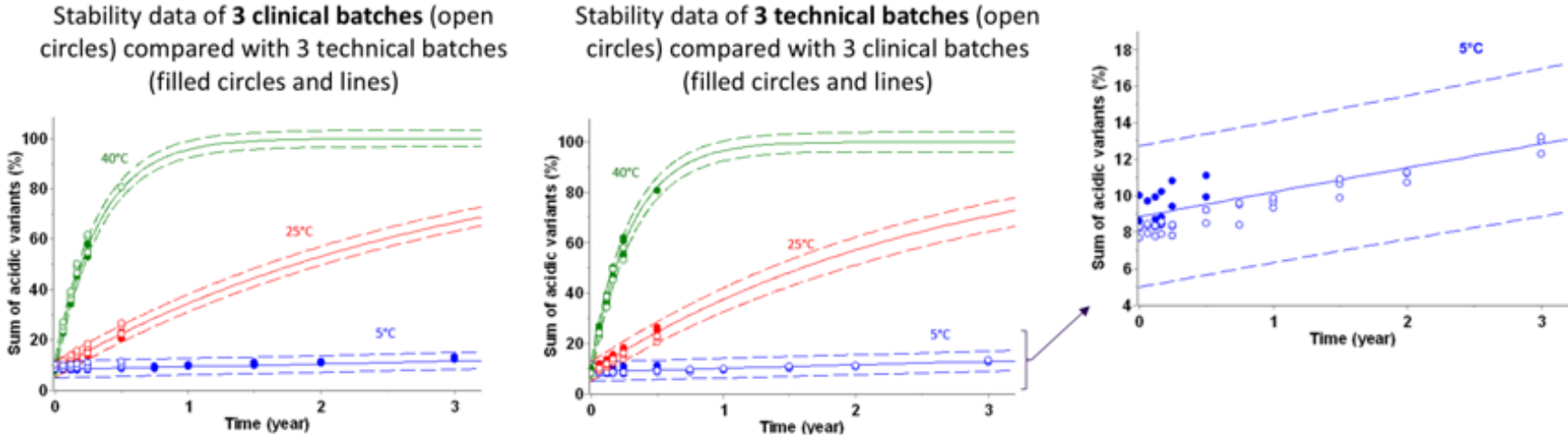


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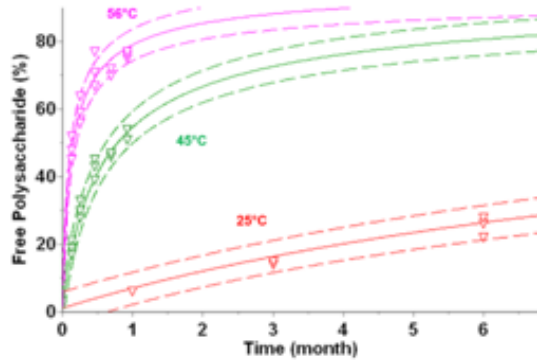
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Advanced kinetic modelling

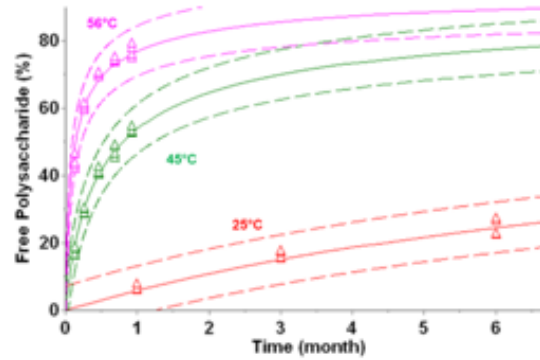


Advanced kinetic modelling

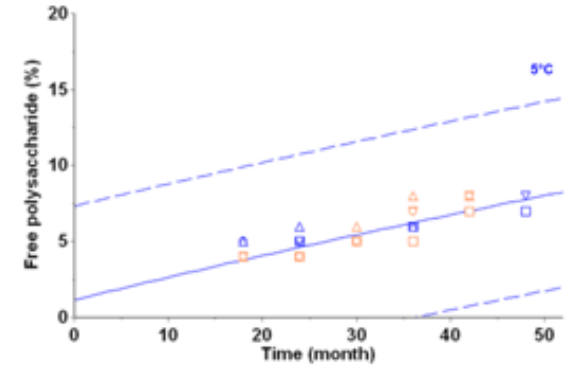
Stability data of **small-scale batch**
(triangles) compared with large-scale batch
kinetic model (lines)



Stability data of **large-scale batch**
(triangles) compared with small-scale batch
kinetic model (lines)



Cross comparisons of experimental data
and model predictions up to 4-years



Conclusion

- Comparability of stability appears less straight forward than for release
- Decision tree proposed considering as much as possible different situations
 - Recommended standard approaches
 - Possible alternative approaches in particular situations

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Thank you

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