



IQ Risk-Based Predictive Stability Modeling Sub-team

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Cliff Enright, *Summer Lights*
Artwork from The Creative
Center at University Settlement

Representatives from industry

abbvie



GlaxoSmithKline



Objectives team

- Capture current models in industry for stability prediction
- Define requirements for acceptable Model types
 - Share data sets to model for evaluation across models
- Define desired outputs – how can the models be applied
- Define appropriate experimental study designs

→ Is it possible to unify industry approaches ?



Current modeling approaches

- Stability models
 - Chemical degradation (some physical)
 - Packaging selection
- Mainly based on Extended Arrhenius Equation
- *ASAPprime*® – Used by approximately majority of companies
- Accelerated Stability Modeling (ASM) – published by GSK*
- Predictive Statistical Stability (PSS) – used at Merck
- Specific in-house developed models

Model comparison – multiple data sets

- Each company provides a data set for modeling by different companies
 - Six companies use *ASAPprime*®
 - Others used in-house developed models
- Discuss outcome of all model predictions
- Compare predicted rates at intended storage condition
- Validate with long term data



Model comparison – multiple data sets

- 20 data sets were modeled by each company
- Predicted rates vary between models
 - Bigger variation with non-linear kinetics
- Need to understand the differences in predictions
 - Evaluate differences observed for *ASAPprime*® users

Possible explanations for difference in *ASAPprime*® predictions

- Choice of Model
 - Default vs Zero order model in case of linear kinetics
 - Model choice depend on:
 - R^2 and Q^2 values
 - Knowledge of degradation kinetics

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 - Apparent outliers
 - No degradation at certain condition / time point
 - Levels far beyond spec limit (significant extrapolation)

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- Different strategy for exclusion of data points
 - Apparent outliers
 - No degradation at certain condition / time point
 - Levels far beyond spec limit (significant extrapolation)
- Different strategy on data below reporting threshold
 - Report as:
 - 0% or reporting threshold
 - Calculated value
 - Leave blank

Model comparison – multiple data sets

Predictions can differ between models

- Model dependent
 - Non linear kinetics more challenging
- Individual differences
 - Exclusion of data points
 - Choice of best fitting model
- Refinement of model with long term data

Review experimental design spaces

- Application of risk-based predictive stability modeling
 - Early development – Late development
 - Allows early understanding of
 - degradation kinetics
 - Impact of T and RH
 - Experimental designs
 - Differences in storage T, RH (General vs Product driven)
 - Time for accelerated testing (days, weeks, months)
 - Number of required data points
- Recommendations for proper design space
- Alignment across industry feasible?
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Perspectives

White paper to address

- Common chemical degradation models
- Overview of potential experimental design spaces
- Stepwise approach for Modeling
 - Determine experimental design space (accelerated conditions, time)
 - Establishment of suitable Model
 - Long term stability prediction
 - Model improvement and re-assessment
- Applications

Shelf life prediction and setting, formulation screening, process comparison, packaging prediction and selection





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