Predictive Stability Approaches to Assess Critical Characteristics in Drug Product Development

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Acknowledgments

• Paul Gerst (Pfizer)

• Ken Waterman (FreeThink Technologies)

• Risk Based Predictive Stability Working Group
Outline

• Background on predictive stability
• Commonly used approaches in Pharmaceutical industry
• Key elements of a predictive stability study
• Case Studies
  • ASAP
  • ASM
  • PSS
What is Predictive Stability?

• Stability studies performed during development that allow for prediction of stability or performance over time
  • Typically ~1-2 months in duration

• Extrapolate kinetic models from the short term timepoints to predict long term stability
  • Requires integration of packaging model to incorporate container humidity over time

• Commonly performed for chemical stability modeling
  • Loss of Assay
  • Formation of degradation products
Accelerated Stability Assessment Program (ASAP)

- Originally published in the early 2000s
- Samples are stored at high temp/RH for ~3-4 weeks
- Follows isoconversion approach for reaching failure
- Based on modified Arrhenius equation:
  \[
  \ln(k) = \ln(A) - \frac{E_a}{R \times T} + B(RH)
  \]
- ASAPprime® software now available from FreeThink Technologies
GSK-Accelerated Stability Modeling (ASM)

- Samples are stored at high temp/RH for ~2 weeks
- Evaluates data against several models to select most appropriate model for stability prediction

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Description</th>
<th>Typical Application</th>
<th>Nonlinear Model (Integrated Form) Used for Fitting:</th>
<th>Limitations</th>
<th>Terms Needed to Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Reaction slows exponentially with time</td>
<td>Reaction rate proportional to a limiting reagent that is close to being consumed</td>
<td>$\alpha = C + K3 \cdot \left(1 - \exp\left(-K1 \cdot \exp\left(-\frac{-K2}{T + 273.15} + \frac{K2}{Tref}\right) \cdot H^{N1} \cdot \Delta t\right)\right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Reaction slows down with time</td>
<td>Diffusion</td>
<td>$\alpha = K1 \cdot \exp\left(-\frac{-K2}{T + 273.15} + \frac{K2}{Tref}\right) \cdot (H)^{N1} \cdot \Delta t + C$</td>
<td>$N2 &lt; 1$</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Reaction is linear with time</td>
<td>Zero order reactions</td>
<td>$\alpha = K1 \cdot \exp\left(-\frac{-K2}{T + 273.15} + \frac{K2}{Tref}\right) \cdot (H)^{N1} \cdot \Delta t + C$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Reaction speeds up with time</td>
<td>Power Law Induction Reactions</td>
<td>$\alpha = K1 \cdot \exp\left(-\frac{-K2}{T + 273.15} + \frac{K2}{Tref}\right) \cdot (H)^{N1} \cdot \Delta t^{N2} + C$</td>
<td>$N2 &gt; 1$</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Reaction speeds up exponentially with time</td>
<td>Nucleation, or reaction rate dependent on product concentration</td>
<td>$\alpha = \exp(C) \cdot \exp\left(K1 \cdot \exp\left(-\frac{-K2}{T + 273.15} + \frac{K2}{Tref}\right) \cdot (H)^{N1} \cdot \Delta t\right)$</td>
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</table>

- Allows to be fit to relative humidity or vapor pressure in the “H” term
Predictive Statistical Stability (PSS)

• Stability conditions are built around the intended long term storage environment of the product using response surface methodology

• Does not assume a model, but data is fit to a multi-linear regression (MLR) with effects determined by standard statistical practices

• Predictions are run after 4 & 8 weeks of storage
Key Elements of a Predictive Stability Study

• Study Design*
  • What are the temperature, humidity, & timepoints?
  • What tests are critical to product stability?

• Data Collection

• Data Analysis and Modeling*
  • Kinetics need to be coupled with packaging configuration

• Desired Output

• Validation of the Model (if desired)
Considerations for Study Design (1)

1. Project specific concerns
   - Phase of development
   - Intent of study
   - Will the data be reported to a health agency?
   - How many batches should be analyzed?

2. Critical Stability Tests
   - Assay loss & degradation has been extensively studied to date
   - Dissolution & physical stability are being investigated as a potential next steps
Considerations for Study Design (2)

3. Condition selection
   - Want to cover low/high temperature & humidity
   - An ideal study would cover a minimum of 6 conditions
     - If previous screening data is available the number of conditions could be reduced
     - Want to be able to build a thorough understanding of the impact RH has on reactivity of the compound
   - Should be careful to avoid form changes during study
     - TGA/DSC screening can help with de-risking
     - Has the potential to significantly effect modeling of performance

4. Timepoints to test
   - Depends on how much risk & rework potential the organization wants to take on
   - Want to avoid excessive degradation
Example of ASAP Study Design

- Allows for understanding the impact of humidity & temperature on product stability
- Additional conditions can be added to build a more thorough landscape
Example of GSK-ASM Study Design

- Skewing the run points slightly reduces the resulting correlation between vapor pressure and temperature in the study without compromising the RH based design.

- Allows either RH or vapor pressure to be fit as the humidity term within the kinetic equations.
Data Analysis

• Kinetics of the change in the product (loss of assay, degradation growth, etc.) should be well understood with respect to both temperature and humidity

• Packaging impact on moisture changes over time needs to be incorporated into the modeling for accurate predictions on shelf-life
Impact of Packaging

Moistures permeate into plastic storage bottles, following a standard permeation model, same process as polymer membranes:

\[ Flux = P \cdot \left( \frac{SA}{\text{thickness}} \right) \cdot (VP_{\text{exterior}} - VP_{\text{interior}}) \cdot \Delta t \]

Where

“Flux” is the water vapor transmission rate,
“P” is the permeability coefficient,
“SA” is the surface area,
“thickness” is the wall thickness,
“VP_{\text{exterior}}” is the water vapor pressure on the exterior of the bottle or capsule film,
“VP_{\text{interior}}” is the water vapor pressure in the interior of the bottle or capsule film and,
“\Delta t” is the change in time.

Permeability coefficients follow an Arrhenius relationship with temperature, and can be calculated at different temperatures using equation 4 (Abdel-Bary, 2003).
Solve for Equilibrium RH on Each Day

• Need to experimentally measure and define models for:
  • Moisture permeation of bottles at varying temperatures.
  • Moisture versus RH relationship of desiccant.
  • Moisture versus RH relationship of dosage form.

• With known initial water content, and known permeation of water for a given day, four equations and four unknowns can be solved to find the equilibrium RH on each day.
  • Water Fraction in air
  • Water fraction in dosage form
  • Water fraction in desiccant
  • Overall mass balance.
Common Pitfalls during Modeling

1. All degradation products should be modeled to determine if they are a risk for failure on stability
   • Allows the selection of the appropriate product for future monitoring

2. The accelerated technique does not accelerate all reactions equally
   • Higher powered protocols & longer studies may be needed for some products as development advances

3. Confidence intervals for the prediction need to be factored in decision making
   • Study design may need to be altered to lessen the noise in the data for certain applications
ASAP Case Study: Study Design

- ASAP study performed comparing stability of solid bacitracin and bacitracin zinc
  - Evaluated stability indicating parameters by HPLC:
    - Loss of Potency for Bacitracin A
    - **Growth of Bacitracin F**

ASAP temperature and relative humidity conditions

Courtesy of FreeThink Technologies, Inc.
ASAP Case Study: Determination of Isoconversion Times for Bacitracin F

Growth of bacitracin F from bacitracin Zn followed diffusion kinetics

Courtesy of FreeThink Technologies, Inc.
### ASAP Case Study: ASAP Model Parameters for Growth of Bacitracin F

<table>
<thead>
<tr>
<th>Peptide form</th>
<th>In A</th>
<th>$E_a$ (kcal/mol)</th>
<th>B</th>
<th>$R^2$</th>
<th>$Q^2$</th>
<th>Mean predicted shelf-life 25°C/60% RH (open)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bc</td>
<td>44.6±4.9</td>
<td>29.2±3.3</td>
<td>0.021±0.007</td>
<td>0.95</td>
<td>0.83</td>
<td>1.0 month</td>
</tr>
<tr>
<td>BcZn</td>
<td>45.8±2.2</td>
<td>32.0±1.5</td>
<td>0.008±0.003</td>
<td>0.98</td>
<td>0.96</td>
<td>6.6 years</td>
</tr>
</tbody>
</table>

- **BcZn** has lower sensitivity to moisture compared to **Bc**.
- **BcZn** is significantly more stable than **Bc**.
- **BcZn** has lower sensitivity to moisture.
- Increased activation energy for **BcZn**.
- Good fit to modified Arrhenius equation.
- More sensitive measure of fit than $R^2$.

*Courtesy of FreeThink Technologies, Inc.*
ASAP Case Study: Fit to Long Term Data of Bacitracin F

Long-term data (squares)  
Modeling predictions (lines)

Courtesy of FreeThink Technologies, Inc.
Multiple formulations were compared in accelerated stability prediction (left), then run in long term stability (right).

Accelerated stability predicted which formulation was going to have the most stable results.
GSK-ASM Case Study: Drug Product 81

- Just eyeballing this accelerated data, surely Impurity 966 is the worst one?
- Eyeballing again, that impurity 102, can’t possibly be a risk, it’s nowhere near the specification limit.
- Lesson #1: Don’t believe that eyeballing data is a good approach. Don’t stop doing an analysis due to little response in the data.
GSK-ASM Case Study: Drug Product 81 Comparison to Long Term Data

- Impurity 102 had a low activation energy, did not accelerate substantially at higher temperatures, but ended up the most critical impurity at lower temperatures.

- Impurity 966 was low risk with high activation energy, and showed little to no increase at low temperatures.

- Points out a problem with the isoconversion approach – low activation energy reactions.
PSS Case Study

Response Surface Methodology: Hydrolysis Reaction

- temp = 25, humidity = 10
- temp = 25, humidity = 35
- temp = 25, humidity = 60
- temp = 30, humidity = 10
- temp = 30, humidity = 35
- temp = 30, humidity = 60
- temp = 40, humidity = 10
- temp = 40, humidity = 35
- temp = 40, humidity = 60

Degrade % Claim vs Time (weeks)
PSS Case Study: Magnified View

Response Surface Methodology: Hydrolysis Reaction

- Core
- Film Coat

<table>
<thead>
<tr>
<th>Temp</th>
<th>Humidity</th>
<th>Degradate %Claim</th>
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<tbody>
<tr>
<td>25</td>
<td>10</td>
<td></td>
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<tr>
<td>25</td>
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PSS Case Study: Degradation Rate
Equation: $y = A_1 \exp(x/t_1) + y_0$

$\chi^2/\text{DoF} = 0.02364$

$R^2 = 0.99411$

$y_0 = -0.0701 \pm 0.06701$

$A_1 = 0.07683 \pm 0.01677$

$t_1 = 13.70602 \pm 0.69819$

Total Degs in 2 Years

%RH (at 30°C)
Conclusions

Predictive stability studies have been used to accelerate pharmaceutical development

- Quicker understand of critical stability attributes
- Guidance in formulation and packaging selection
- Choice of long term storage conditions

Study design and integration of packaging models plays a key role in accurate stability predictions
Questions

For follow up questions/discussions:

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References

