Advanced Modeling from Highly Accelerated Stability Testing (ASAP) to Determine Product Shelf-life

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Outline

• ASAPprime® Basic Principles
  • Isoconversion
  • Moisture Sensitivity
  • Statistics

• Packaging

• Regulatory Experience

• Conclusions
Complex Kinetics

• >50% Products show complex kinetics: cannot be fit to simple linear approach
  • Heterogeneous systems
  • Secondary degradation
  • Autocatalysis
  • Inhibitors
Complex Kinetics—Example

Drug → primary degradant → secondary degradant
Traditional Accelerated Stability

‘k’ = Slope of line

**Spec. Limit**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Rate Constant</th>
<th>Rate of Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>70°C</td>
<td>k=0.8/21</td>
<td>0.04%/d</td>
</tr>
<tr>
<td>60°C</td>
<td>k=0.6/21</td>
<td>0.03%/d</td>
</tr>
<tr>
<td>30°C</td>
<td>k=0.05/21</td>
<td>0.0024%/d</td>
</tr>
</tbody>
</table>
Traditional Accelerated Stability

Appears very non-Arrhenius

Impossible to predict shelf-life from high T results

More unstable

70°C

60°C

30°C

ln k

1/T

0.0029 0.003 0.0031 0.0032 0.0033

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Isoconversion Accelerated Stability

- Isoconversion: Time to “edge of failure”
- Time to **specification limit** (specific degradant, total degradant, potency, color change, etc.)

![Graph showing Isoconversion](image)

- 70°C: $k = \frac{0.5}{3} = 0.17\%/d$
- 60°C: $k = \frac{0.5}{11} = 0.045\%/d$

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**Isoconversion**: Time to “edge of failure”

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Accurate predictions do not depend on the kinetic form
Humidity Corrected Arrhenius Equation

\[ \ln k = \ln A - \frac{E_a}{(RT)} + B(RH) \]

- **ln** \( k \): natural logarithm of the reaction rate constant \( k \)
- **ln A**: collision frequency
- \( E_a \): activation energy
- \( RT \): product of the gas constant \( R \) and temperature \( T \)
- **B(RH)**: humidity sensitivity factor
- \( 1.986 \text{ cal/deg} \): conversion factor
- **Spec. limit/(isoconversion time)**: specific limit or isoconversion time
- **equilibrium relative humidity**
Typical $E_a$ and $B$ values

Drug Products and APIs Studied at FreeThink

Average 27 kcal/mol

Average 0.04

RH sensitivity does not indicate hydrolysis!
## Impact of B Factor on Shelf-Life

<table>
<thead>
<tr>
<th>B</th>
<th>60%RH in PVC Blister</th>
<th>65%RH in PVC Blister</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 low moisture sensitivity</td>
<td>5.0 yrs</td>
<td>5.0 yrs</td>
</tr>
<tr>
<td>0.04 average moisture sensitivity</td>
<td>5.0 yrs</td>
<td>3.8 yrs</td>
</tr>
<tr>
<td>0.09 high moisture sensitivity</td>
<td>5.0 yrs</td>
<td>3.0 yrs</td>
</tr>
</tbody>
</table>
Accelerated Stability Assessment Program (ASAP) Design of Experiment: Determining the Plane

\[ \ln k = \ln A - \frac{E_a}{RT} + B(RH) \]
Estimation error bars increase with T extrapolation: fast stability studies (high T) are accurate, but lead to large error bars.
Experimental Setup

Mini-chambers:

Ball Mason jars
Hold seals even at 95°C

Saturated salt slurry: in vial with GoreTex cover

Sample

T/RH data logger
Packaged-Product Stability

Moisture transfer depends on **MVTR + ΔRH**

Moisture inside packaging equilibrates between headspace (RH), tablets, desiccant (**vapor sorption isotherms**)

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Relative Humidity as a Function of Time

Exactly predicted from easily measured information:

1. MVTR
2. moisture sorption isotherm
3. headspace volume
4. external RH, T
Predicted (Lines) vs. Measured RH

500 mg tablets 60-cc HDPE Bottles (40°C/75%RH)

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Example 1

Drug Product Tablets; 30°C/65%RH

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Example 2

Tablet Product at 25°C/60%RH in Bottles with Desiccant

%Degradant vs Time (yrs)

ASAP\textit{prime}® prediction

Real Time

B = 0.02

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## Example 3—Nicorette® Lozenge

<table>
<thead>
<tr>
<th>Condition (PVdC blisters)</th>
<th>Shelf-life (mos) ASAPprime® mean predicted</th>
<th>Shelf-life observed (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25°C/60%RH</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>30°C/65%RH</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>30°C/75%RH</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>40°C/75%RH</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*L. Chen, S. Faust, A. Venkatarangan (GSK Consumer Health) AAPS Poster 2013*
Example 4: Peptide Stability

Lines are ASAPprime® mean predicted loss of active with dotted lines representing one standard deviation. Squares are measured values.

Example 5: Formulation/Process Development

<table>
<thead>
<tr>
<th>Tablet</th>
<th>$E_a$ (kcal/mol)</th>
<th>B</th>
<th>%Probability of passing @2 yr, 30°C/65%RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>0.04</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>0.06</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>0.04</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>0.03</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>0.04</td>
<td>9</td>
</tr>
</tbody>
</table>

Tablet 2 was only one without wet-granulation. Program shifted to avoid water exposure of drug.
Example 6—75-cc HDPE bottles 25 capsules/bottle—Model vs. Measured

25°C/60%RH

#3 gelatin capsule

S. Thielges, Janssen 2013
Example 7
IV Formulation (Cold Storage)

From H. Williams presentation “Science of Stability Conference” Boston 2018
## More Examples

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
<th>ASAPprime®</th>
<th>Measured</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled release tablet</td>
<td>9 mos. 25°C/60%RH</td>
<td>4.2±0.84%</td>
<td>4.1%</td>
<td>Hydrolysis; Esterification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.2±0.24%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>IR tablet; GTI</td>
<td>3 mos. 25°C/60%RH</td>
<td>6.2±1.0 ppm</td>
<td>5.3 ppm</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Oral solution</td>
<td>2 yrs. 30°C</td>
<td>0.40±0.08%</td>
<td>0.31%</td>
<td>Lactamization</td>
</tr>
<tr>
<td>Patch</td>
<td>6 mos. 40°C</td>
<td>1.19±0.24%</td>
<td>1.72%</td>
<td>Acetyl formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.88±0.17%</td>
<td>0.89%</td>
<td>Hydroxy formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.12±0.08%</td>
<td>0.15%</td>
<td>Formamide formation</td>
</tr>
<tr>
<td>Immediate release tablet</td>
<td>4 yrs. 25°C/60%RH</td>
<td>0.22±0.06%</td>
<td>0.22%</td>
<td>Lactamization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.07±0.02%</td>
<td>0.06%</td>
<td>Lactonization</td>
</tr>
<tr>
<td>Capsule product</td>
<td>2 yrs. 25°C/60%RH</td>
<td>0.08±0.00%</td>
<td>0.08%</td>
<td>Lactamization</td>
</tr>
<tr>
<td>Oral solution</td>
<td>7 mos./5°C</td>
<td>0.60±0.03%</td>
<td>0.56%</td>
<td>Hydrolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.36±0.01%</td>
<td>0.35%</td>
<td>Hydrolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.61±0.03%</td>
<td>0.47%</td>
<td>Hydrolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.30±0.02%</td>
<td>0.32%</td>
<td>Hydrolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.69±0.03%</td>
<td>0.53%</td>
<td>Hydrolysis</td>
</tr>
</tbody>
</table>

*Colgan, et al. (Pfizer), (J. Pharm. Innov.)*

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# ASAP Regulatory Experience (Clinical) by Country

![Bar chart showing the number of submissions to regulatory agencies by country. The chart compares the total accepted and total submitted.](chart.png)

- **USA**
- **Ukraine**
- **UK**
- **Turkey**
- **Taiwan**
- **Sweden**
- **Spain**
- **Russia**
- **Portugal**
- **Poland**
- **Netherlands**
- **Moldova**
- **Malaysia**
- **Lebanon**
- **S. Korea**
- **Kenya**
- **Italy**
- **Ireland**
- **India**
- **Hungary**
- **Germany**
- **Georgia**
- **France**
- **Finland**
- **Egypt**
- **Denmark**
- **China**
- **Canada**
- **Bulgaria**
- **Brazil**
- **Belgium**

*From F. Qiu presentation “Science of Stability Conference” Boston 2018*
Conclusions

• Accelerated stability can be applied effectively to set shelf-life with ASAPprime® using:
  • Isoconversion
  • Accounting for moisture sensitivity
  • Adapting statistics

• ASAPprime® enables better decisions, faster