Implementing an Accelerated Stability Assessment Program: Case Study

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With Special Thanks to Jeff Hofer, Timothy Kramer, Chad Wolfe, Seungyil Yoon, Steve Baertschi and Ken Waterman

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IVT's Third Annual Forum on Stability Programs

Lilly

Answers That Matter.

Agenda

Accelerated Stability Assessment Program (ASAP)

- Overview and Background
- Study design
- Integrating ASAP with package modeling to predict product stability

Implementation - How Lilly is Currently Implementing the Program

- Accelerated stability template tools
- General process flow
- Considerations when performing an ASAP study
- Case Studies

Continuous Improvement - How Lilly is Improving the Program

- ASAP working group
- Process improvements
- ASAP*prime*™ software

Background

- Arrhenius stability modeling has been used successfully within the industry
- Lilly has not fully leveraged these stability tools and approaches
- Pfizer has demonstrated a rapid, lean, and highly efficient approach to chemical stability screening that involves non-traditional times/storage conditions and statistical design and analysis of those experiments
- A business process and associated tools have been developed to leverage this approach

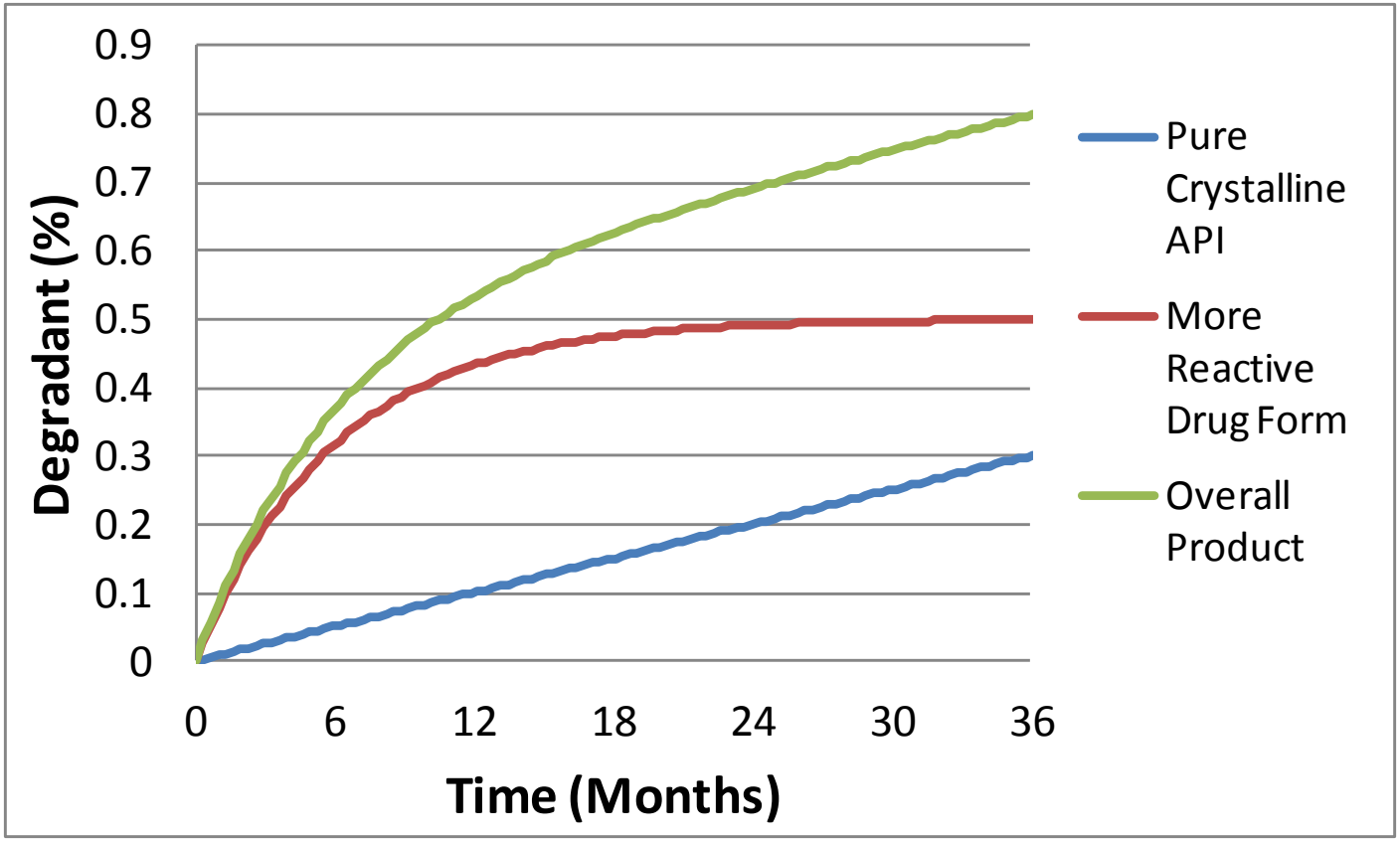
Accelerated Stability Assessment Program (ASAP) Overview

- Modeling tool used in development that improves product degradation understanding
- Has been shown in the literature to provide credible predictions for shelf life/product expiry estimations
- Faster than conventional stability and package screening studies
- Scope
  - Small molecule solid drug products, APIs, excipients

Why Accelerated Stability?: Potential Benefits

- Increased Scientific understanding of degradation mechanisms
- Specification rationale for purity
- Increased clinical start times
- Reduction of ICH stability re-dos
- Reduction of package screening studies prior to registration stability
- Flexibility for post-approval changes to stability commitments
- Can be used specifically in early in development to
  - compare prototype formulations
  - identify stability issues (i.e. utilized as part of Genotoxic Impurities (GTI) control strategy process in development)
  - support risk assessment decisions for excipients
  - identify proposed storage conditions
  - identify acceptable CT packaging

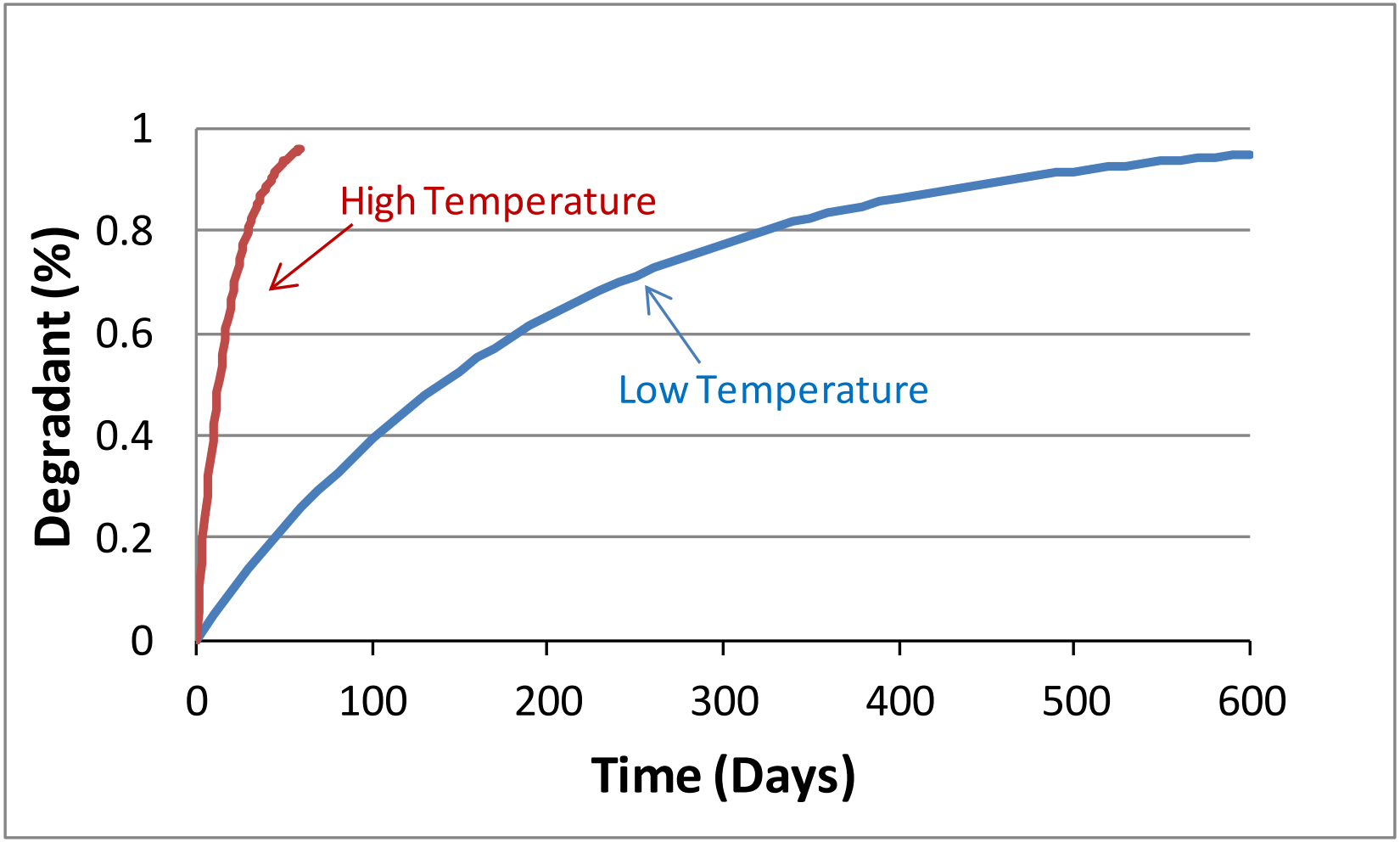
Heterogeneous Kinetics for Solids



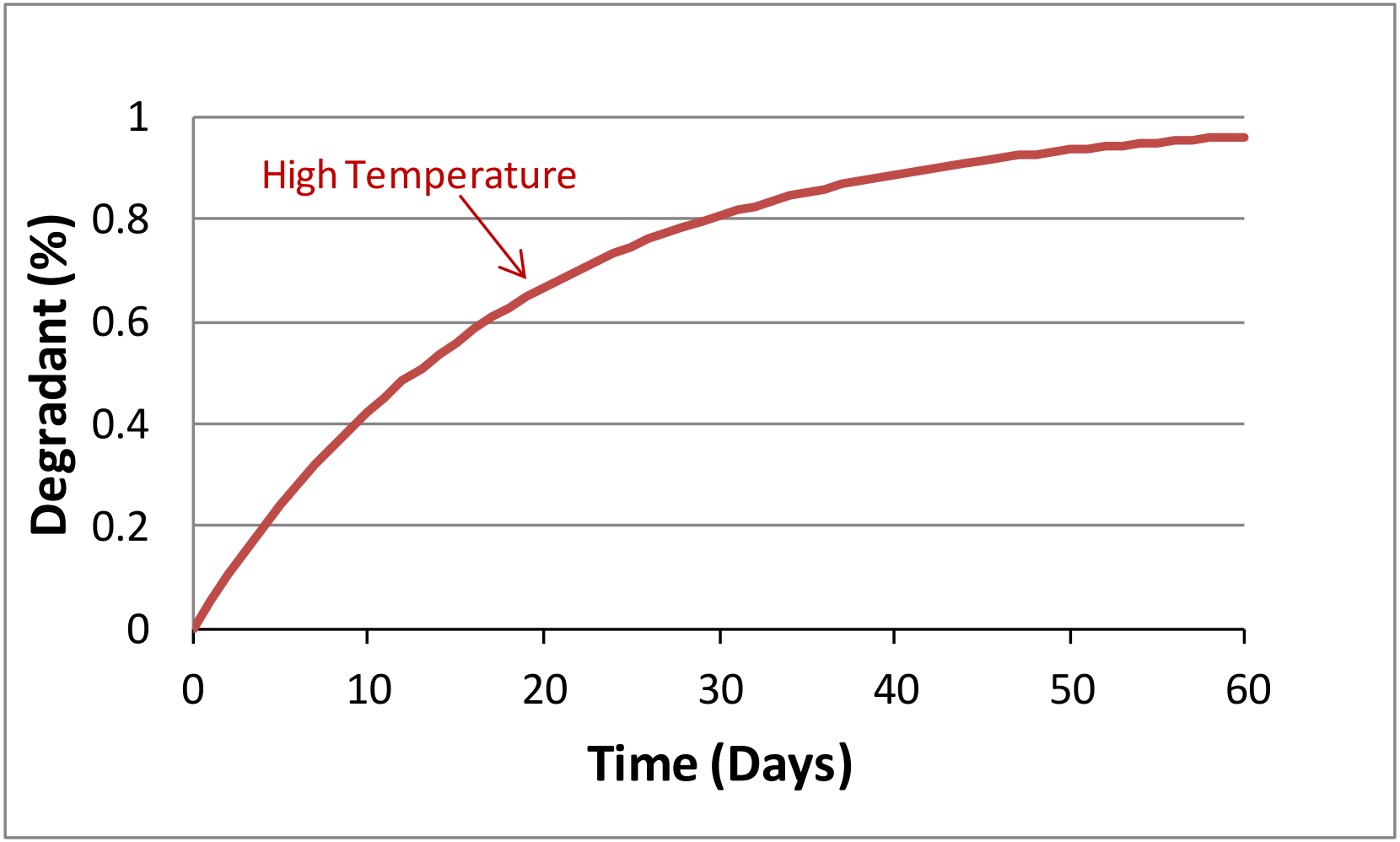
$$[Drug]_{Crsytalline} \underset{k_2}{\overset{k_1}{\rightleftarrows}} [Drug]_{Reactive} \xrightarrow{k_3} [Degradant]$$

$$k_4$$

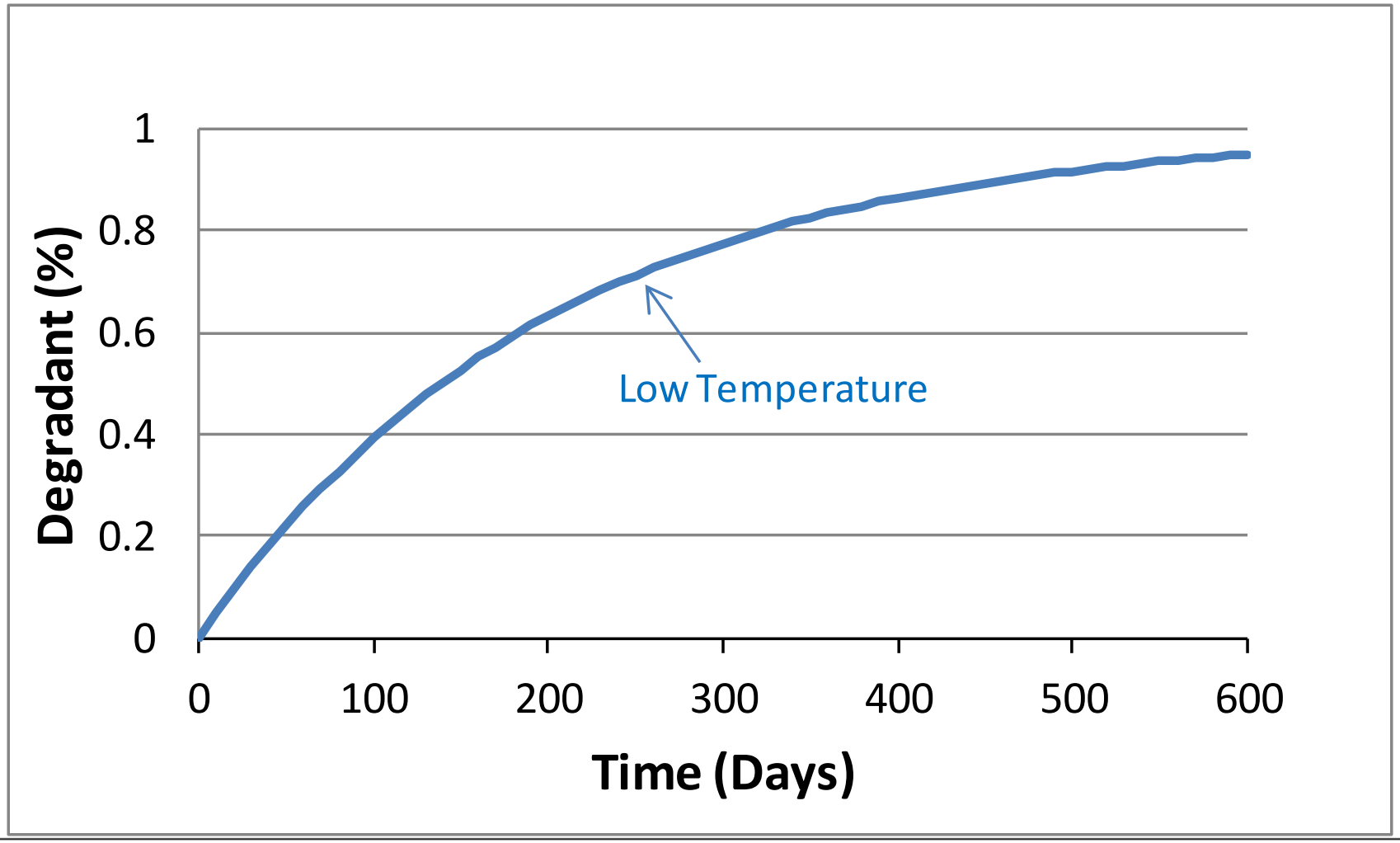
Stability at Different Temperatures



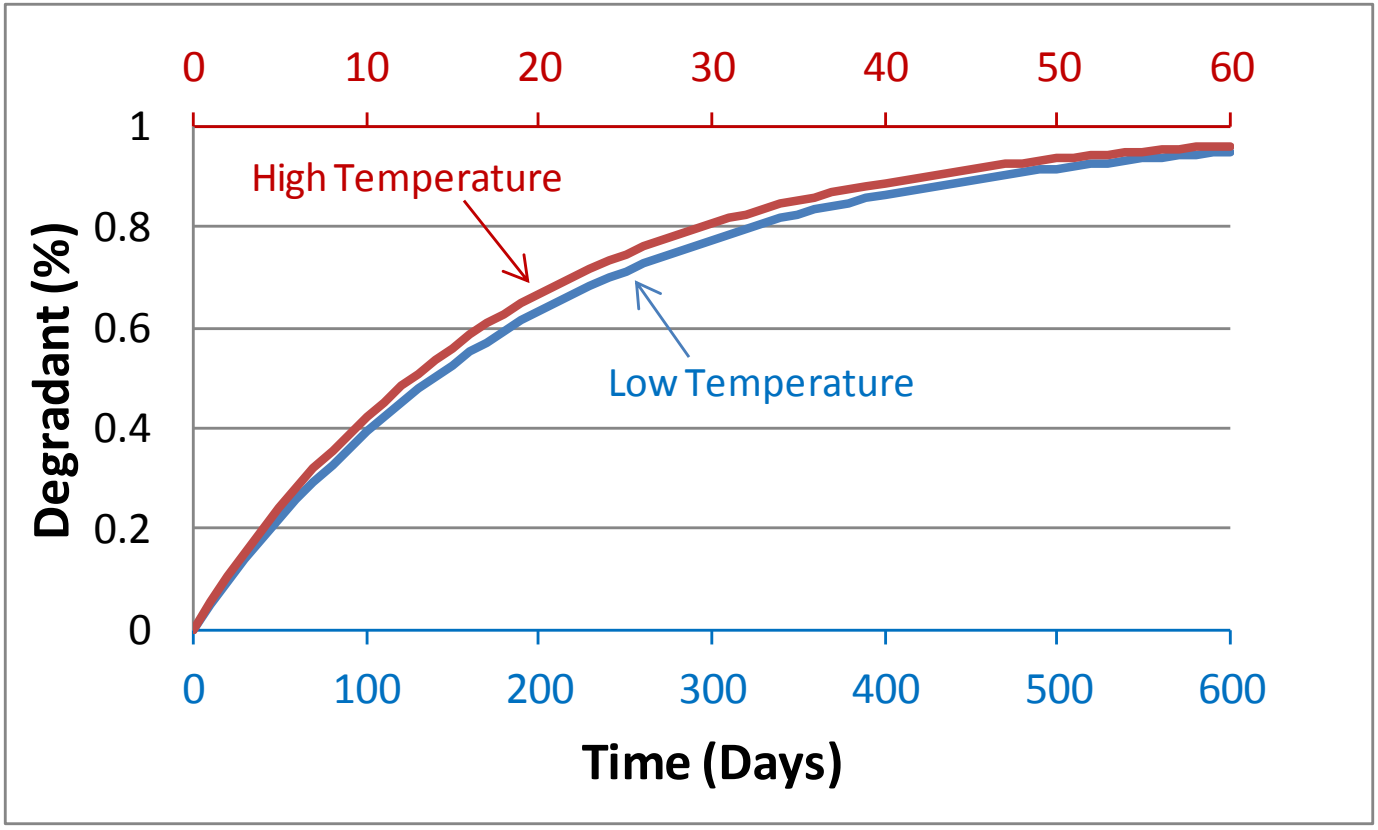
Stability at High Temperature



Stability at Low Temperature

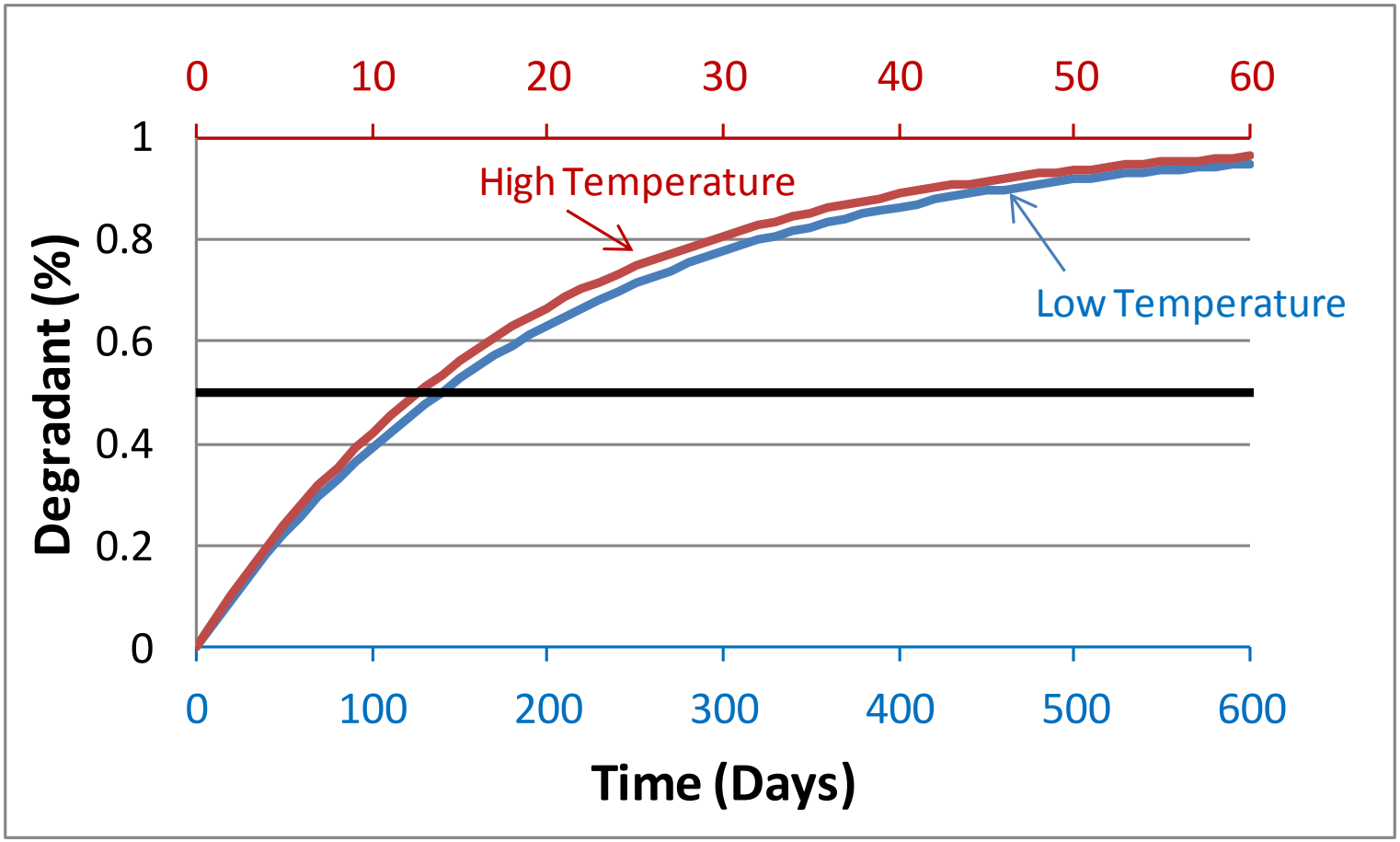


Stability at Different Temperatures



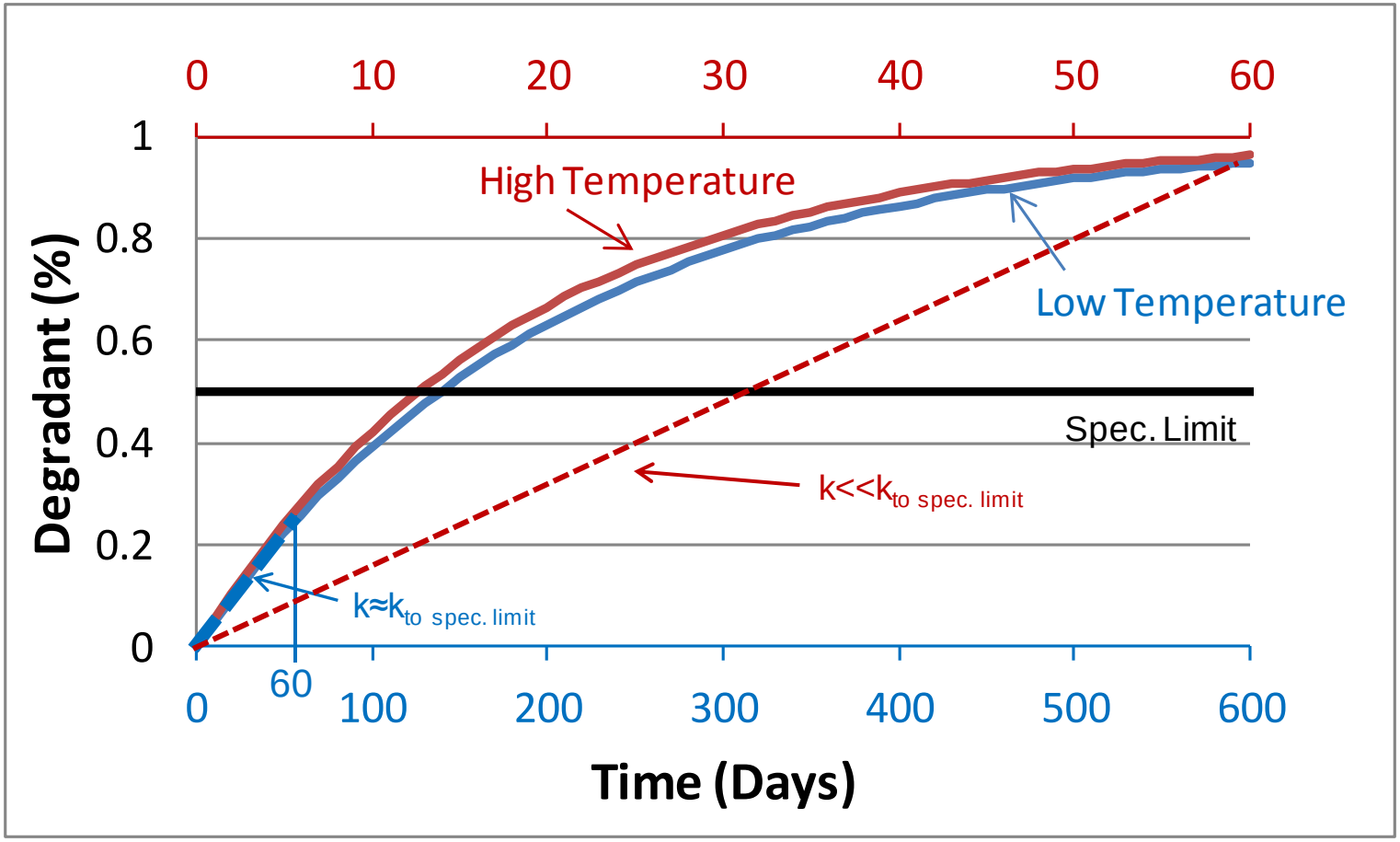
- The shape of the degradation increase depends on the amount of degradation not on temperature (Isoconversion)
- The rate of the reaction depends on temperature

Stability at Different Temperatures: Historical Approach



- Historical approach: The time axis is fixed independent of the actual degradant level

Stability at Different Temperatures: Historical Approach



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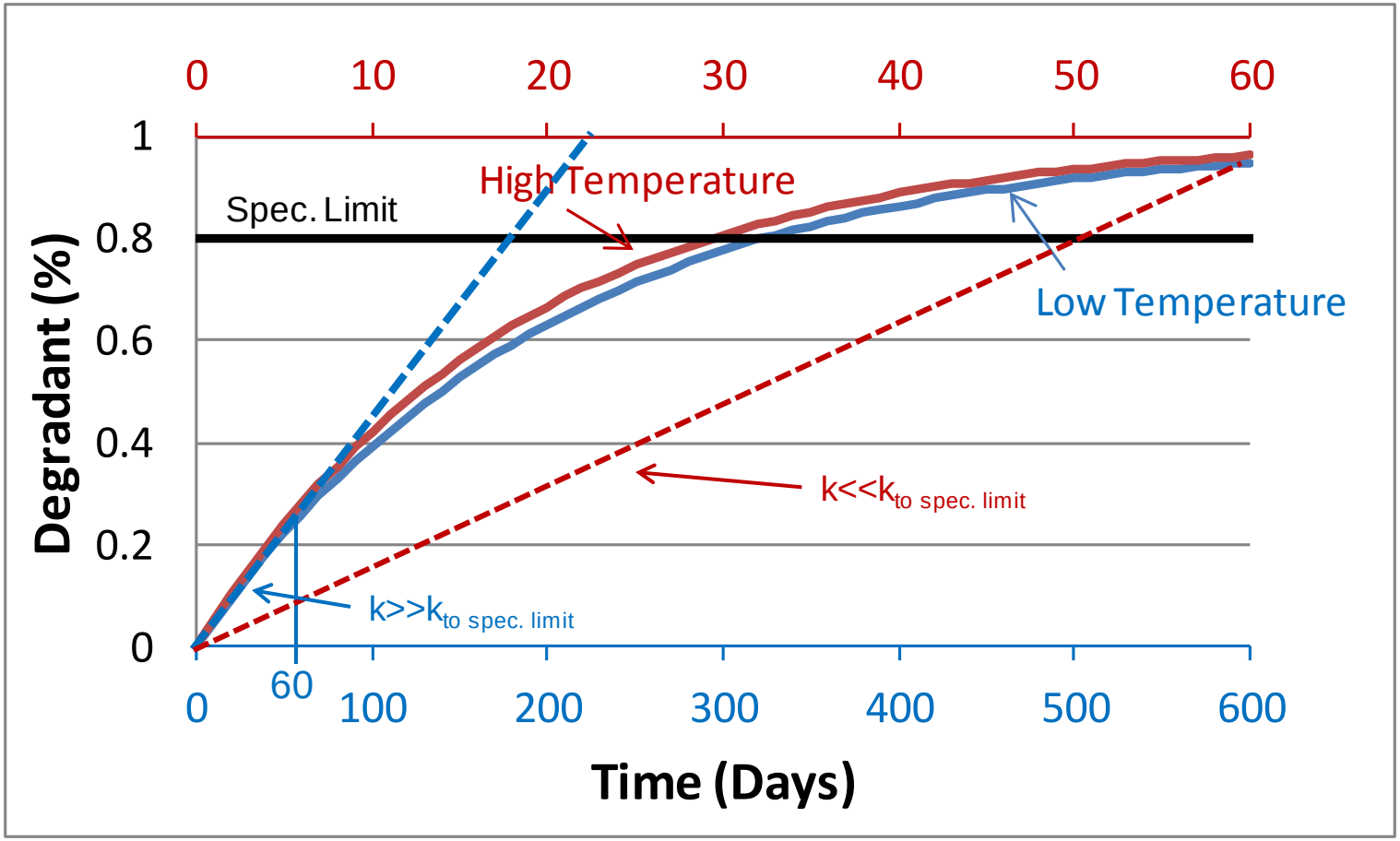
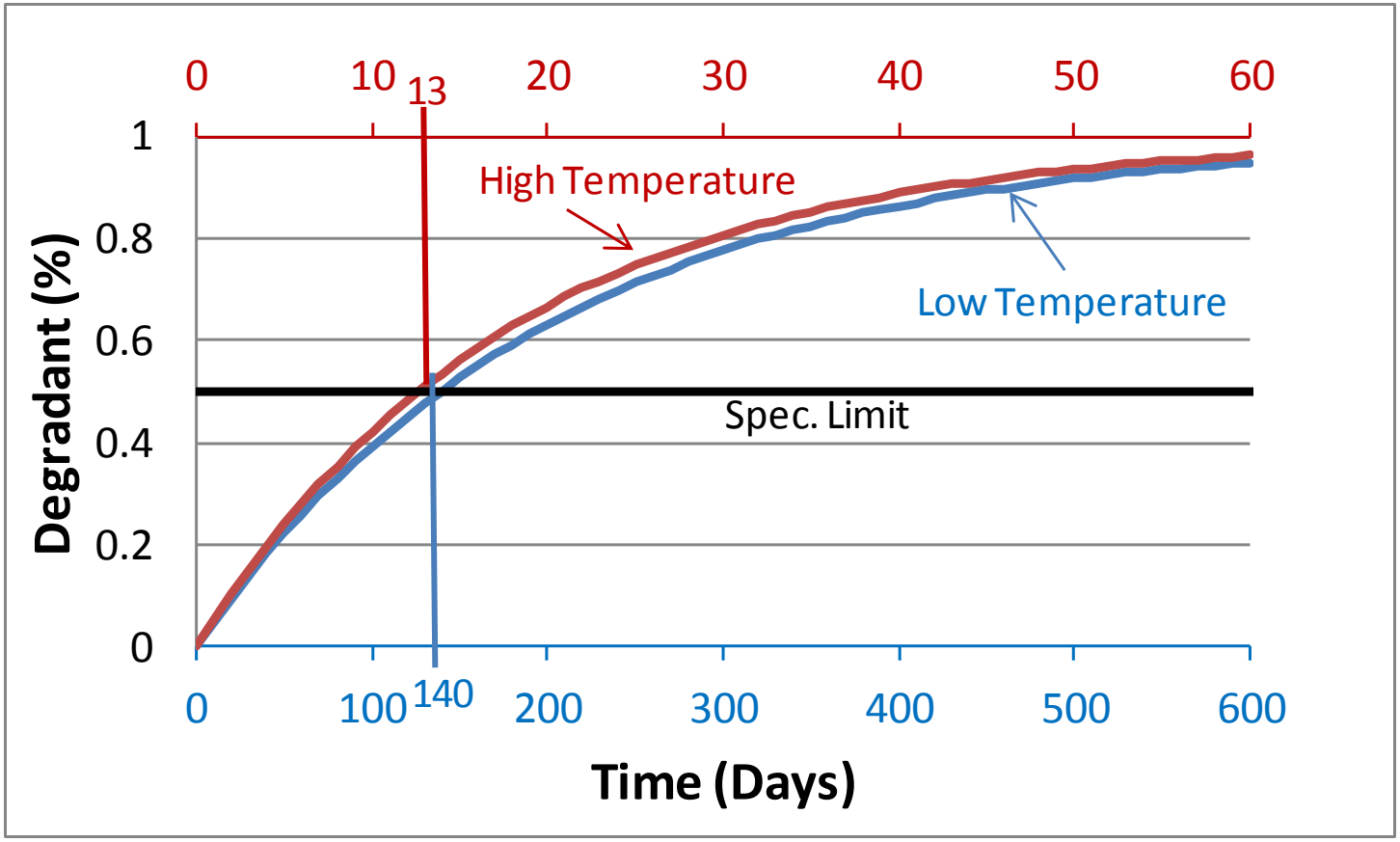
Stability at Different Temperatures: Historical Approach



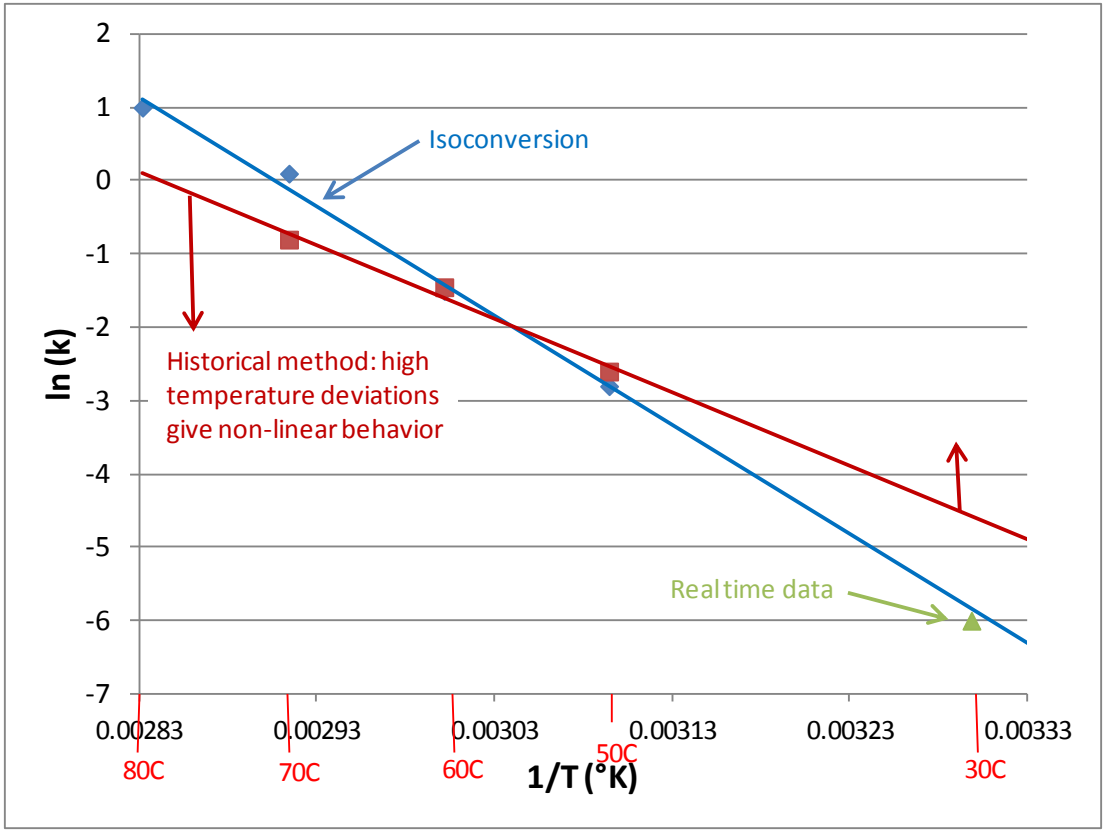
- Historical approach: The time axis is fixed independent of the actual degradant level

Stability at Different Temperatures: ASAP (Isoconversion) Approach



- ASAP approach: Adjust time to target an amount of degradation equal to the specification limit at each condition

Example Comparison Historical and Isoconversion Approaches When Reactive Drug Form is Present



Plot kindly provided by Ken Waterman. Example found in Waterman, K. C.*et. al.* "Improved Protocol and Data Analysis for Accelerated Shelf-Life Estimation of Solid Dosage Forms." *Pharmaceutical Research 24* (2007) 780-790

- Using the historical approach results in a prediction of worse extrapolated lower temperature stability than is actually observed

Arrhenius Model

$$k = Ae^{-E_a / RT}$$

$$\ln(k) = \frac{-E_a}{R} \times \frac{1}{T} + \ln A = f\left(\frac{1}{T}\right)$$

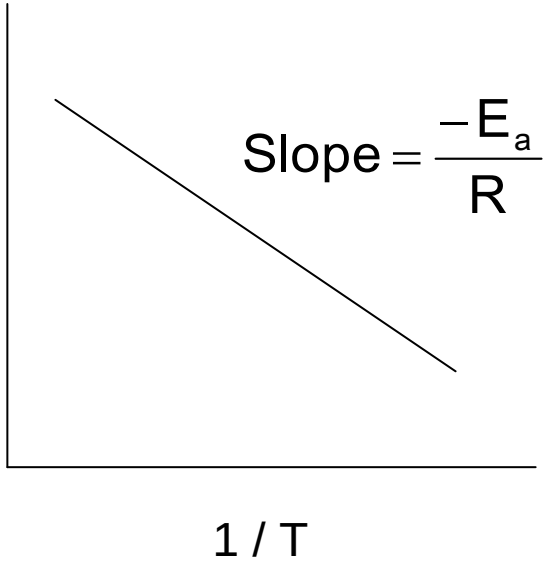
k = Reaction rate, estimated from data for each of the five conditions

E_a = Energy of Activation (kcal mol^{-1})

R = Gas constant (kcal mol^{-1} K^{-1})

T = Temperature in °K

A = Pre-exponential Factor



Humidity Corrected Arrhenius Equation

activation energy

humidity sensitivity factor

$$\ln(k) = \frac{-E_a}{R} \times \frac{1}{T} + \ln A + B(ERH)$$

1/(isoconversion time)

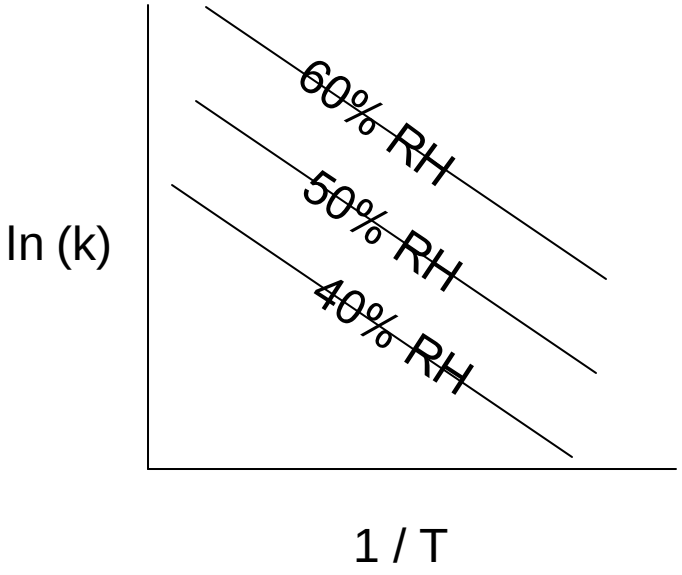
collision frequency

equilibrium relative humidity

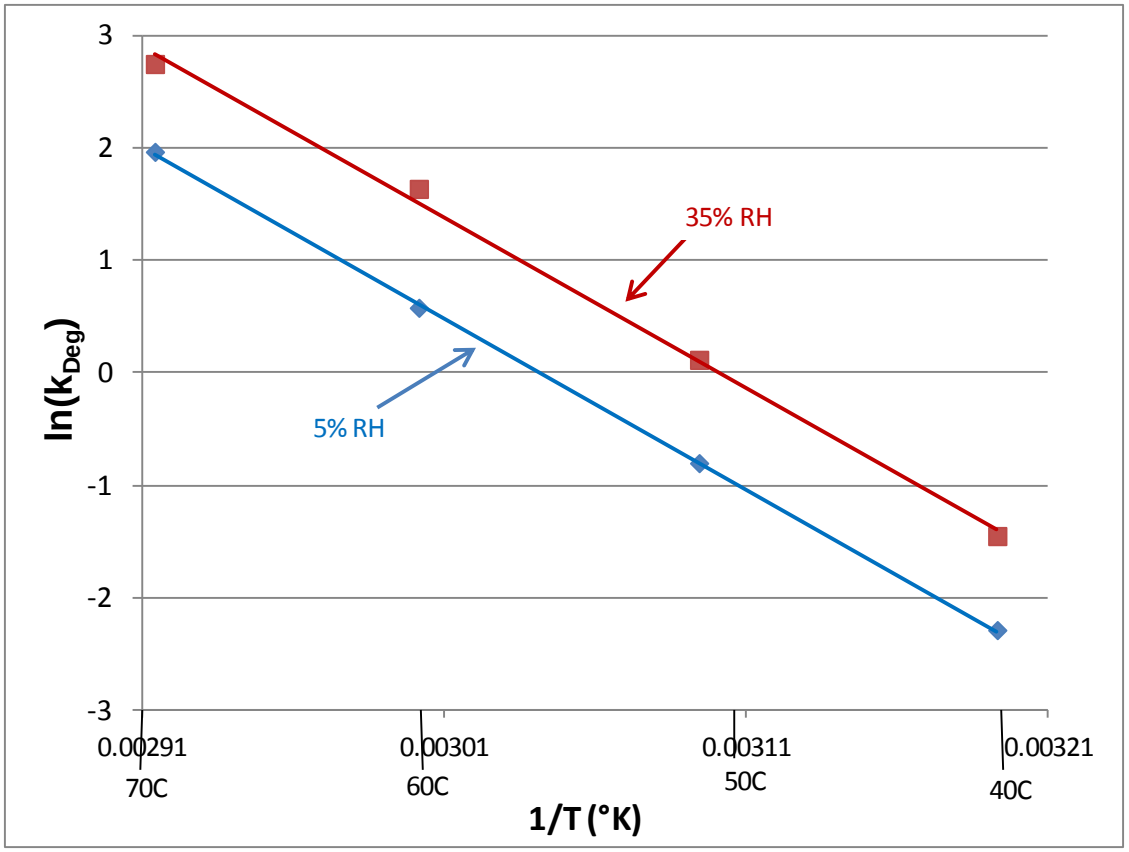
Relative humidity in testing should be less than the critical relative humidity (CRH)

Above CRH, sample dissolves, changing phases – not representative of lower RHs.

(CRH is the humidity above which samples deliquesce)

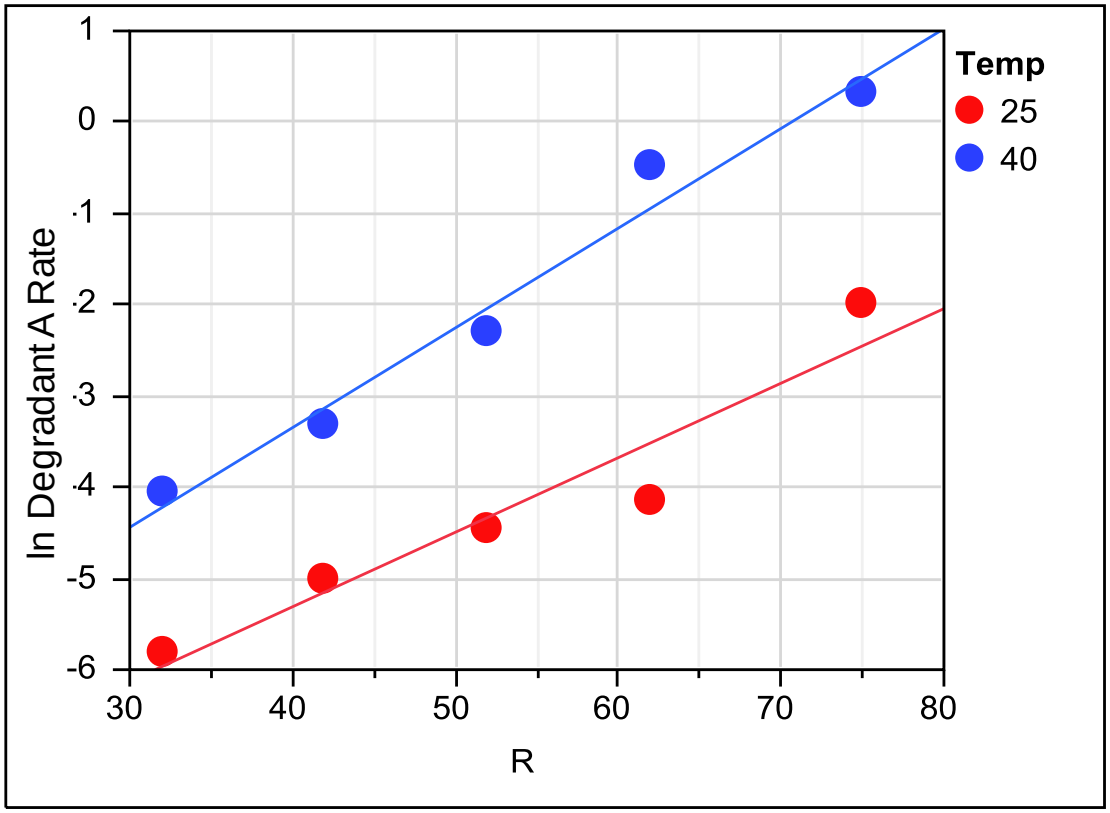


Effect of Temperature on Degradation Rates



- Linear relationship between the ln k_{Deg} and 1/Temp
- Parallel Arrhenius curves observed at each RH level

Effect of Relative Humidity on Degradation Rates



- Linear relationship between the ln $k_{Degradant\ A}$ and RH
- Nearly parallel Arrhenius curves observed at each temperature

Effect of B Values on Shelf Life (Constant Temperature)

B	60%RH Bottle with Desiccant (10% Effective RH)	60%RH Open Bottle	65%RH Open Bottle	75%RH Open Bottle
0.00 Low Moisture Sensitivity	3 years	3 years	3 years	3 years
0.04 Average Moisture Sensitivity	3 years	149 days	122 days	82 days
0.08 High Moisture Senstitivity	3 years	21 days	14 days	7 days

Increasing the RH by 50% (10 to 60%RH) results in a 7 fold decrease in stability with an average B value of 0.04

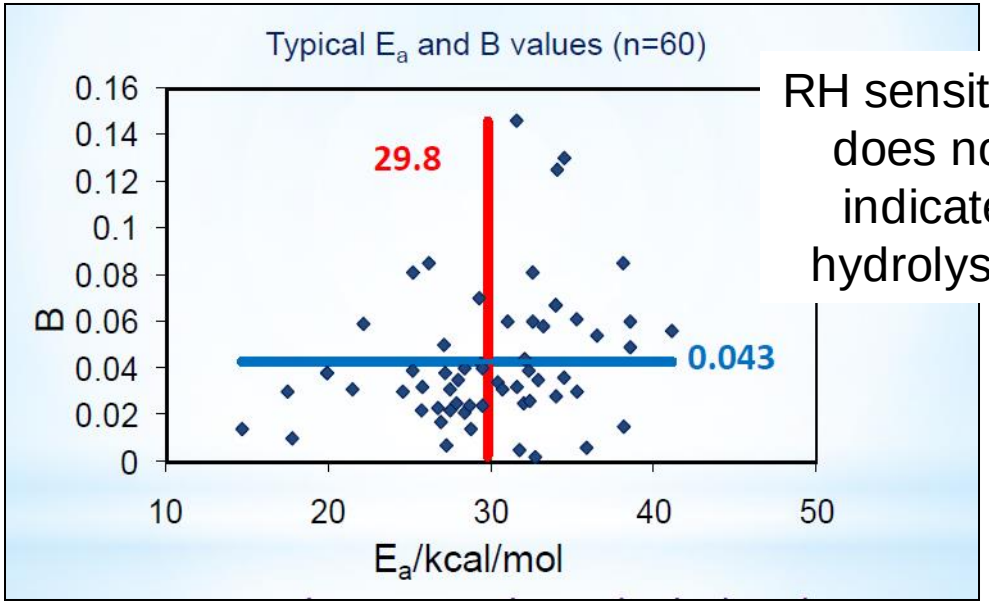
Effect of Activation Energies on Shelf Life (Constant RH)

Shelf-Life (Years)			
Ea (kcal/mol)	**25°C**	**30°C**	**40°C**
17 Low Activation Energy	3.0	1.9	0.8
30 Average Activation Energy	3.0	1.3	0.3
41 High Activation Energy	3.0	1.0	0.1

The higher the activation energy, the more sensitive the product is to changes in temperature

Typical E_a and B Values

- Pfizer has used the ASAP approach to evaluate 60+ compounds



RH sensitivity does not indicate hydrolysis!

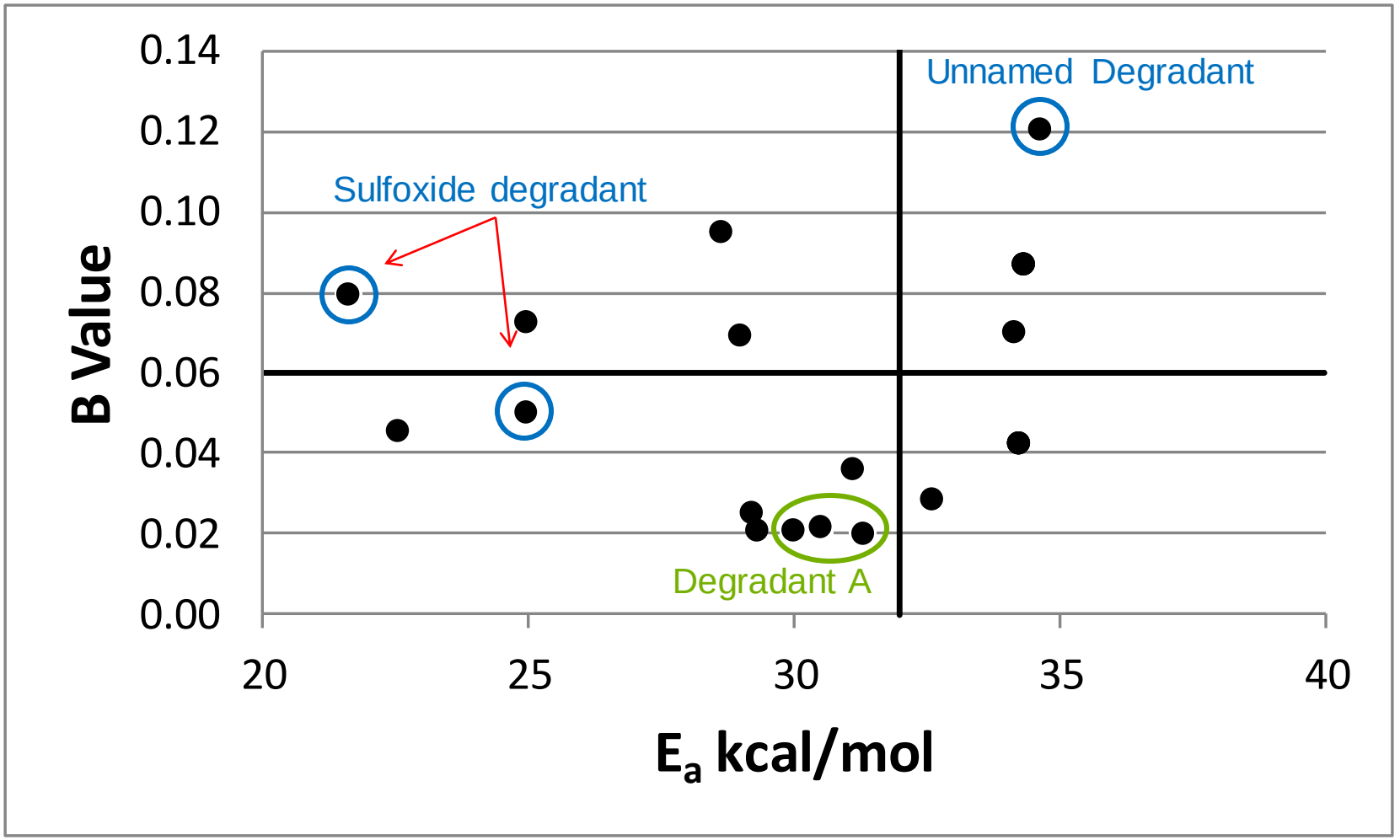
- E_a values
  - Range: 17 – 41 kcal/mol
  - Average: 30 kcal/mol
- B values
  - Average: 0.04
  - Range: 0 – 0.15 (all but 3 B values ≤ 0.08)

Plot kindly provided by K. Waterman

Summary of E_a and B values for ASAP Studies Performed at Lilly

- ASAP studies have been performed on 7+ different compounds at various stages of development
- Earlier versions of Arrhenius modeling using historical time based methods were also performed on several formulations/compounds
- Total impurities and/or individual impurities were modeled for those compounds
- Several products that have been evaluated are very stable and have shown little to no degradation during ASAP studies – good problem to have?
- E_a values
  - Range: 23 – 35 kcal/mol
  - Average: 32 kcal/mol
- B values
  - Range: 0.02 – 0.12
  - Average: 0.06

Summary of E_a and B values for ASAP Studies Performed at Lilly



Case Study A
Case Study B

Typical Proposed ASAP Screening Protocol

Temperature (C)	%RH	Days
50	75	14
70	75	1
60	40	14
80	40	2
70	5	14

- **Design product specific protocol if existing data available**
- Data generated only at the initial and endpoint for each condition
- May run multiple initials to get a good estimate of the initial value
- Sample start times can be staggered so that they all end at the same time to minimize assay variability
- The standard design does not incorporate an oxygen effect but this can be studied if relevant

Study Analysis

- Rate of change data modeled to provide estimates of temperature and RH effects
- Estimates can be used to compare formulations and support risk assessment decisions for excipients including supporting excipient selection or continued excipient use
- External humidity protection provided by packaging
  - Change in RH over time for package is combined with degradation estimates to generate predicted degradation profiles for each package and storage condition combination and support initial container closure selection strategy

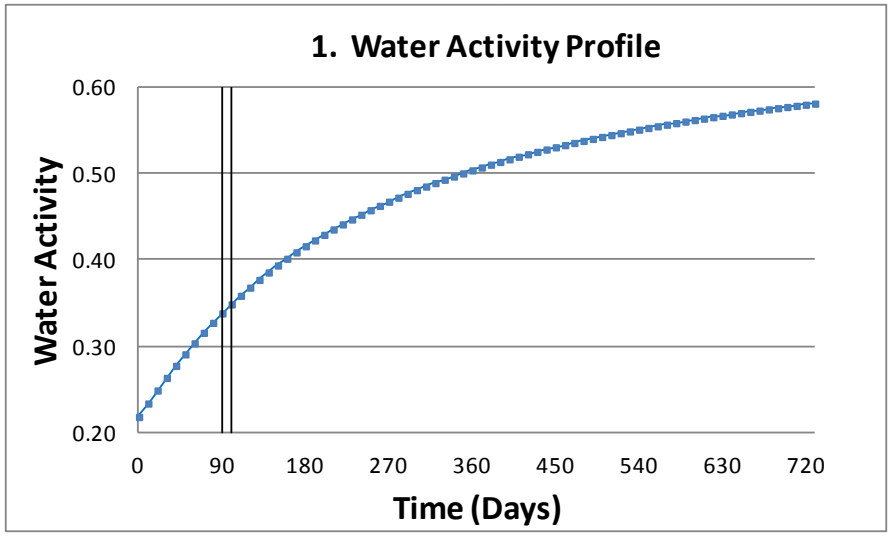
Approach to Combining Product Degradation Kinetics with Package Modeling

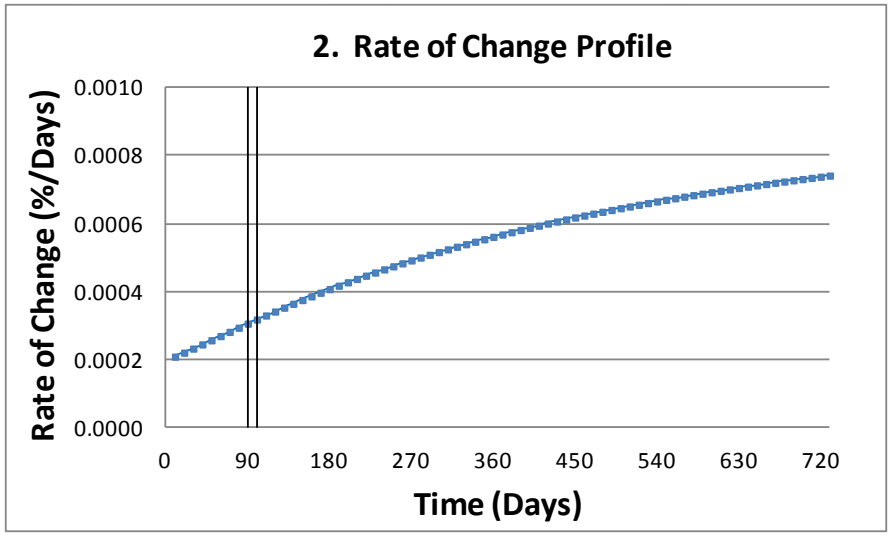
- For each potential package at each temperature, moisture uptake profile obtained
- Combine:
  - the rate of change information with
  - the information on the moisture uptake of a given package for
  - various control strategies (e.g., different initial moisture content levels) to generate a predicted stability profile at a given storage condition

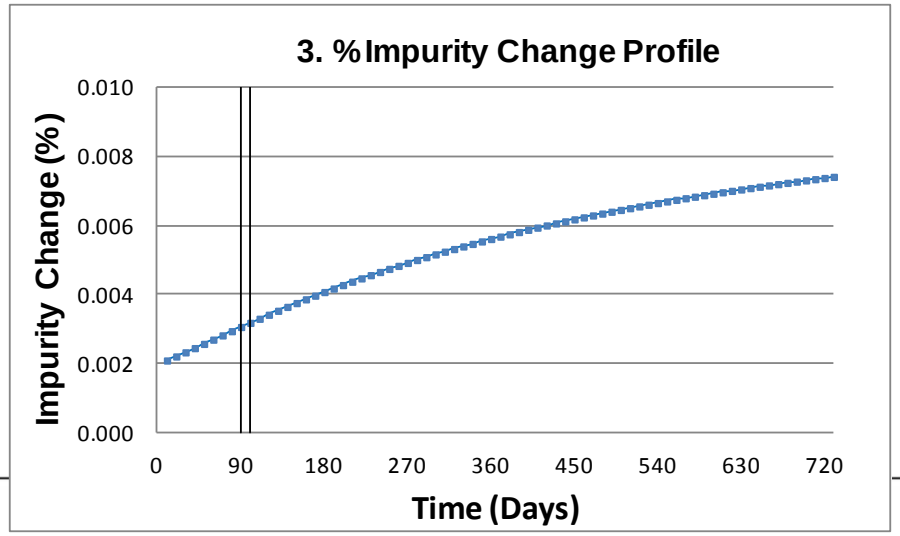
Approach to Combining Product Degradation Kinetics with Package Modeling

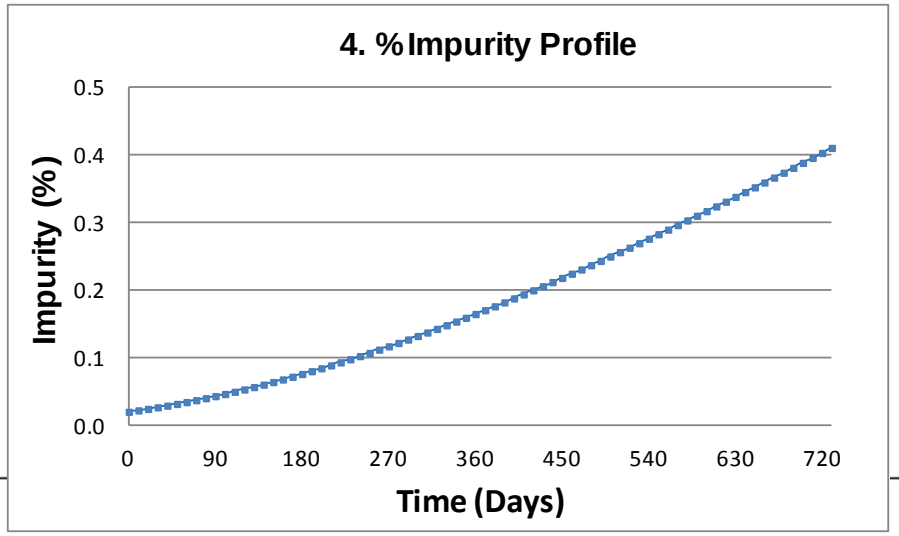
- For a fixed storage condition (temp. and RH) and an initial water activity setting, for each fixed time interval (1 day, 1 week, 10 days, etc.) calculate
  - Water activity level
  - Estimated rate of degradation for that water activity level
  - Estimated impurity change in that time interval
  - Cumulative amount of the impurity

Approach to Combining Product Degradation Kinetics with Package Modeling









Product-Packaging Stability Modeling

Product

- Moisture sorption isotherm (GAB, Langmuir models)
- **Product degradation kinetics (From ASAP)**

Package

- Permeability (Fick's laws of diffusion)

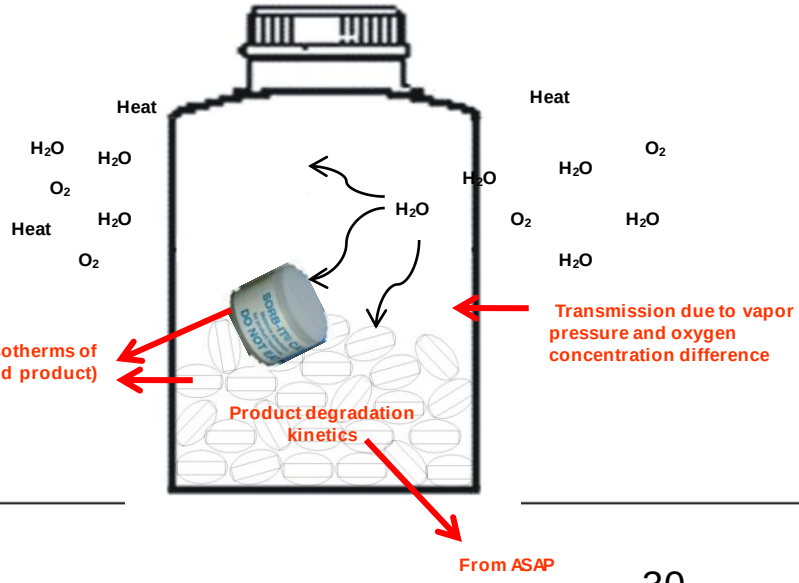
Product-Packaging Stability Modeling

Environment

- Partial pressure for moisture, oxygen, etc.

Experimentally determined inputs (material properties)

- Packaging – moisture (and oxygen) permeability
- Product – initial moisture content, moisture sorption isotherms for solids, and product degradation kinetics (ASAP)
- Environment – relevant storage conditions



Modeled Outputs

- Water activity (Relative humidity)
- Moisture contents of solids (product and/or desiccant)
- Impurity levels and profiles

How Lilly Implemented the Program…

- Small group of scientists and statisticians assembled to assess ASAP and develop a pilot process/implementation plan
- Information repository developed that included literature articles (or references) and presentations to help educate scientists/statisticians
- A defined process and Excel based tools were developed to facilitate implementation
- Integration with existing package modeling tools

Accelerated Stability Template Tool

- Non-validated Excel Spreadsheet
- Assumes that only an initial and final time point are collected for each storage condition
- Calculates the coefficients for the parameters (intercept, temperature, and RH) which serve as inputs into the packaging tool to determine the feasibility of packages
- Calculates a coefficient for oxygen if studied
- Uses named ranges, allowing the coefficient estimates to be compiled into a database

Tool Inputs: Descriptive Information

Color Codes:
User input
Critical Data
Calculation
Instructions

Enter information into tan cells	
Batch or Lot Number	ABC123
Stability Reference Number	12345
VP Page Set Reference	ABCDE
LY Number	LY123456
Molecule Name	Compound X
Other Descriptors	20 mg tab
Degradation Product	Hydrolysis Deg A
Retention Time (if appropriate) [min]	1.23
Test Method Reference Number	B12345
ASRD Contact Person	Suzie Stability
Reference Date	July 22, 2011
Increasing or Decreasing Response?	Increasing
Rows of data to use in regression and plots (excluding initial)	5

Tool Inputs: Test Data

Color Codes:
User input
Critical Data
Calculation
Instructions

Compound X - 20 mg tab: Hydrolysis Deg A								
Target Days	Target Temperature (°C)	Measured Temperature (°C)	Target RH	Target Oxygen (%)	1/T	Measured Aw	Measured O2	Measured Hydrolysis Deg A
0	Initial		Initial		- NA -			0.000
14	50	49	75	21	0.003104	0.72	21	0.017
14	60	60	40	21	0.003002	0.36	21	0.015
14	70	70	5	21	0.002914	0.17	21	0.059
1	70	70	75	21	0.002914	0.74	21	0.014
2	80	80	40	21	0.002832	0.34	21	0.023

- Tool is pre-populated with the standard screening protocol
- More than just five conditions can be input into the tool
- Conditions can be made product specific

Tool Output: Regression Coefficients

Color Codes:
User input
Critical Data
Calculation
Instructions

Results:	
Compound X - 20 mg tab: Hydrolysis Deg A	
Intercept (daily rate)	31.6908
Intercept (monthly rate)	35.1086
Slope: Reciprocal Temperature	-13,028.6
Slope: Oxygen	0.0000
Slope: Water Activity	2.6620
R-squared	94.78%

These coefficients get incorporated with packaging information to predict impurity levels for packaged products

Tool performs a regression to estimate relevant coefficients

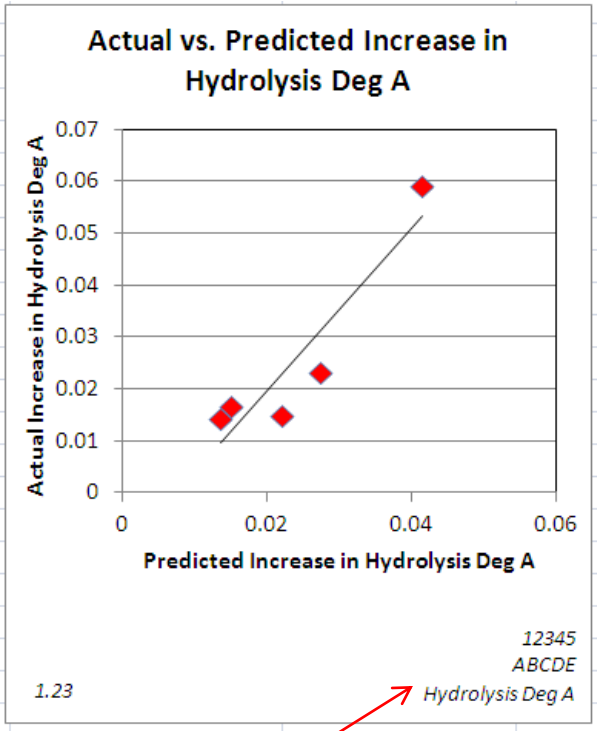
Tool Output: Custom Predictor

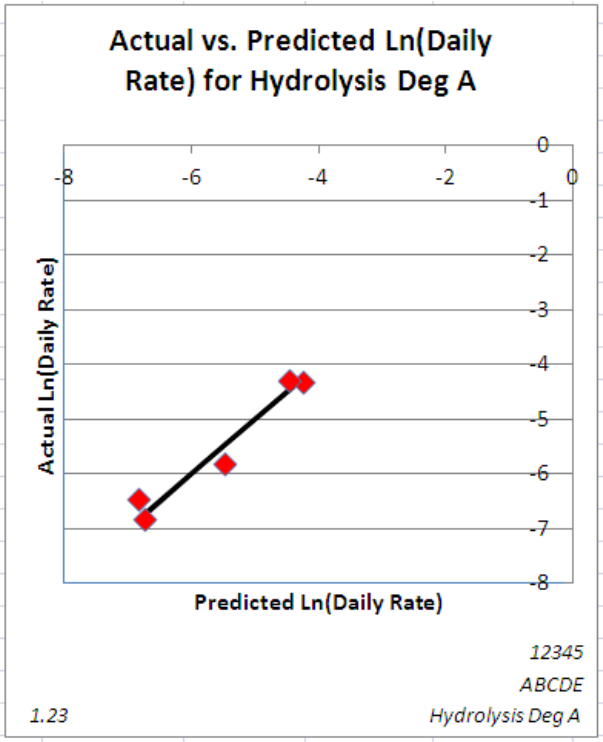
Predicted Values	Hydrolysis Deg A	Initial Level
25°C/60%RH 1 year	0.011	0.000
25°C/60%RH 2 years	0.022	
25°C/60%RH 3 years	0.033	
30°C/65%RH 1 year	0.026	
30°C/65%RH 2 years	0.052	
30°C/65%RH 3 years	0.078	
40°C/75%RH 6 months	0.067	

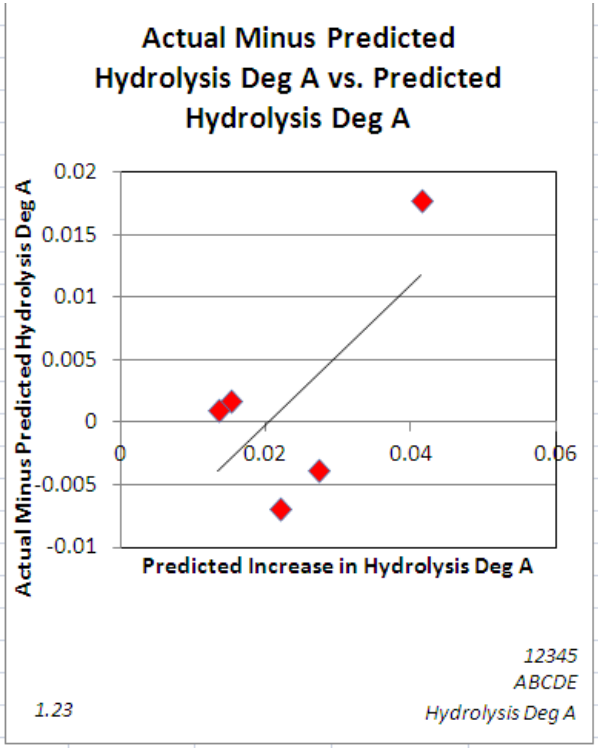
Custom Predictor: (enter temp, RH, and years below)						
Temp [°C]	RH [%]	Time (yrs)	Deg A	Slopes	Label	
						Insert additional rows here (if needed)

- Tool allows user to input specified temperature and humidity conditions for a specified time and returns predicted impurity level and rate of impurity formation
- Model assumes conditions are similar to “open dish” and not dynamically changing as they would with packaging

Tool Outputs: Summary Graphs







Footers linked to the descriptive information

Graphs generated to evaluate how good the model fit is

Follow Up Study Design to Improve Estimates

- Consult with team statistician
- If the five conditions result in large differences in the amount of degradation observed, use preliminary rate estimates to design a more informed follow up study
    - Obtain improved estimates by selecting accelerated conditions that generate similar degradation levels (isoconversion)
    - Follow up Study Design Tool
        - Inputs
            - Targeted amount of degradation (specification)
            - Initial parameter estimates for y-intercept, temperature and RH effects
            - Max number of days for study
        - Outputs
            - Temperature/RH combinations (in 5°C/5% RH units) capable of achieving targeted change within allotted time
            - Product specific design is selected to allow for new (improved) estimates of the temperature and RH effects

General Process Flow

1. Design study, write protocol
2. Obtain and place samples in chambers at target RH at the specified temperature for each condition
3. Pull samples at specified times and hold under defined conditions
4. Assay initial and stressed samples on same run (reduced analytical variability)
5. Enter results into LIMS system and into modeling spreadsheet tool
6. Store spreadsheet in eLN and prepare for data transfer to database
7. Evaluate results to determine whether a follow-up study is needed. If running a follow-up study, use the development tool to identify conditions for follow-up study and repeat steps 1-6
8. Provide coefficients to the package modeling EXCEL spreadsheet for prediction in different package configurations
9. Also provide existing data to compare to the model predictions

Considerations When Performing an ASAP Study

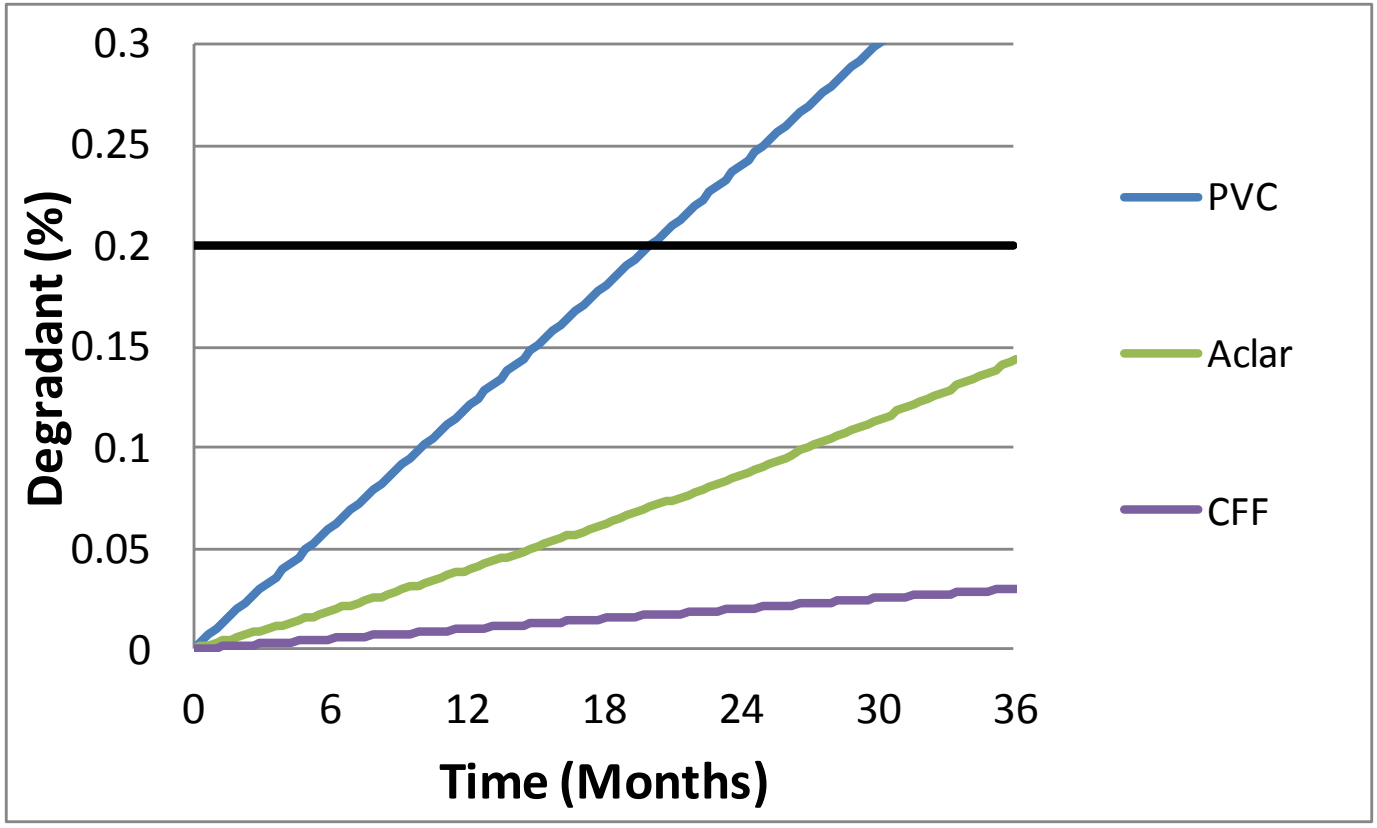
- Stability predictions are most accurate for the isoconversion point which is generally chosen as the degradant's specified or anticipated limit (specification)
- Coefficient estimates are specific to the impurity that was modeled and the formulation that was used
  - Coefficient estimates need to be calculated for each impurity of interest
  - If the formulation changes, the study must be repeated with the new formulation to estimate formulation specific coefficients
- Consider potential failure modes (e.g. Form/Phase change caused by melts, glass transitions, anhydrate/hydrate formation)
- ASAP paradigm focuses on chemical degradation and is not intended for physical changes such as dissolution due to the potential non-Arrhenius behaviors of these properties

Impact on Control Strategy and Design Space

Predictive models can be used to address different manufacturing control strategies and package configuration combinations

- What if initial water activity was lower or higher?
- Would more protective packaging allow a higher initial water activity?
  - If yes, is it worth the additional cost?
- Would less protective packaging be possible if the starting water activity were lower?
  - How big of an impact is this?

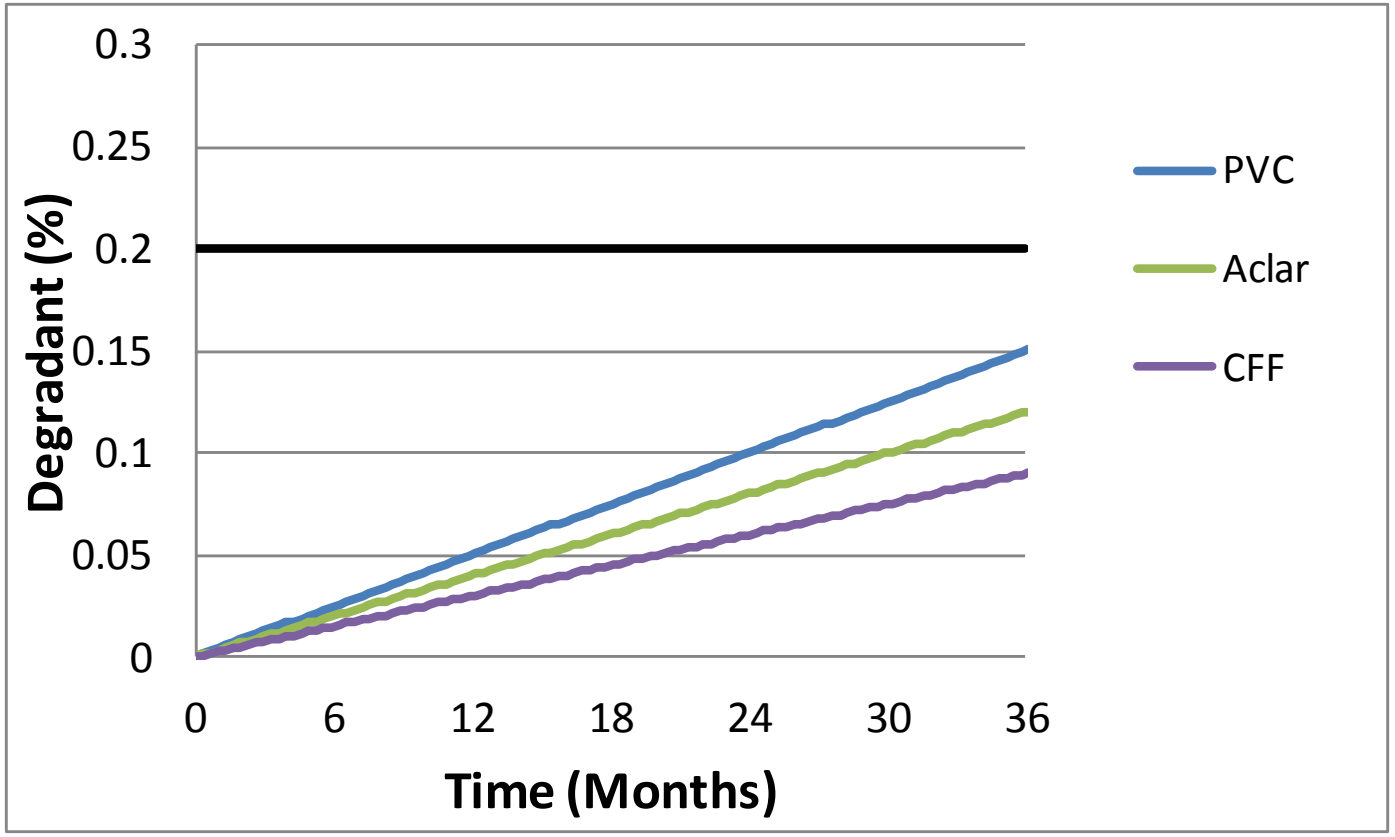
Using Product-Packaging Modeling to Guide Packaging Selection



- B = 0.07, 25°C/60%RH

High B values make the product very sensitive to packaging

Using Product-Packaging Modeling to Guide Packaging Selection



- B = 0.01, 25°C/60%RH

Low B values make the product insensitive to packaging

Case Study A : Background

- Traditional Open dish study (time based historical approach)
  - At the time of the original open dish study, the commercial image was not finalized and ASAP hadn't been implemented
  - Bracketed drug loads for multiple dose strengths
  - Used degradation rates to develop refined ASAP protocol
- Performed ASAP round 1 study (targeting 0.2% isoconversion)
  - 3 strengths (2 formulations)
    - 6 and 12 mg with 3% drug load
    - 18 mg with a 9% drug load
  - Degradant A and Total modeled
- Combined modeled coefficients with package modeling

Special Thanks to Tim Kramer and Seungyil Yoon for Case Study A information contributions

Case Study A : ASAP Round 1

Study Conditions and Results

Formulation	Target Days	Target Temp. (°C)	Actual Temp. (°C)	Target RH	Actual RH (chamber)	6mg Deg A (NMT 0.5%)	12mg Deg A (NMT 0.5%)	18mg* Deg A (NMT 0.5%)
3 and 9% Drug Load (6, 12, and 18 mg Tablets)	0	-	-	-	-	0.017	0.000	0.000
	23	60	60.0	11	0.11	0.137	0.133	0.044
	17	50	49.4	70	0.68	0.125	0.112	0.038
	4	60	60.0	75	0.75	0.109	0.094	0.035
	6	70	68.1	11	0.08	0.130	0.116	0.037
	3	70	69.0	40	0.35	0.148	0.141	0.048

- 6, 12 (3% drug load), and 18 mg (9% drug load) did not achieve target isoconversion level of 0.2% (chosen based on historical stability data not the proposed specification)
- 6 and 12 mg show isoconversion at about 0.12%

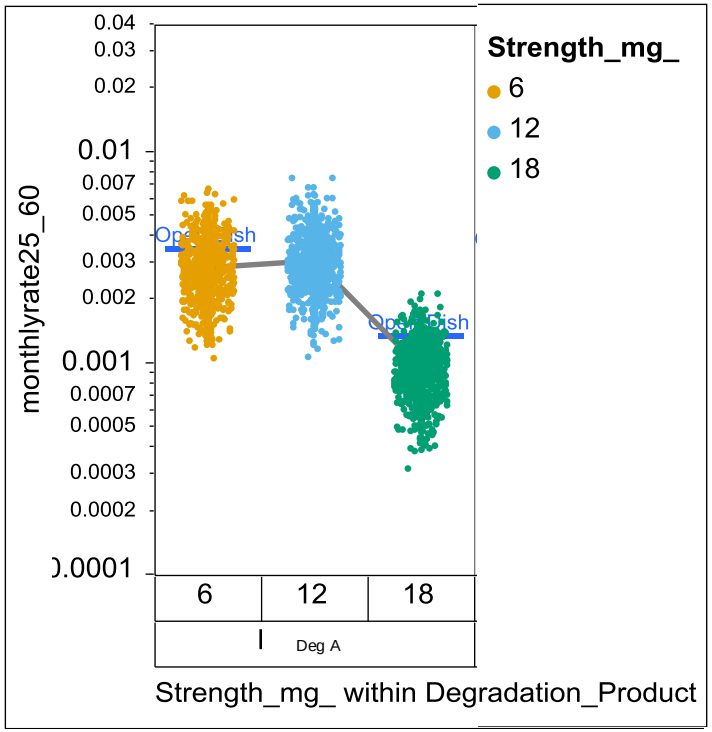
Model Coefficients

Formulation	Analytical Property	Intercept (Monthly Rate)	Coefficient for 1/T	Ea (kcal/mol)	Coefficient for RH (B Term)
3 and 9% Drug Load (6, 12, and 18 mg Tablets)	**6mg Deg A**	44.0778	-15321.6	30.4	0.024
	12mg Deg A	42.7299	-15176.2	30.1	0.023
	18mg Deg A	43.8142	-15593.7	31.0	0.025

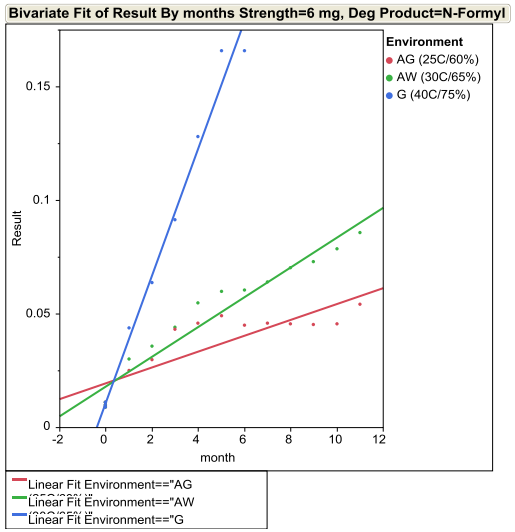
- Coefficients are degradant specific and formulation specific
- The E_a values are close to the average of what has been historically observed
- The B values are within the expected range of 0 – 0.08 (on the low end ~0.02)

Case Study A Results: ASAP Comparison to Traditional Open Dish Data

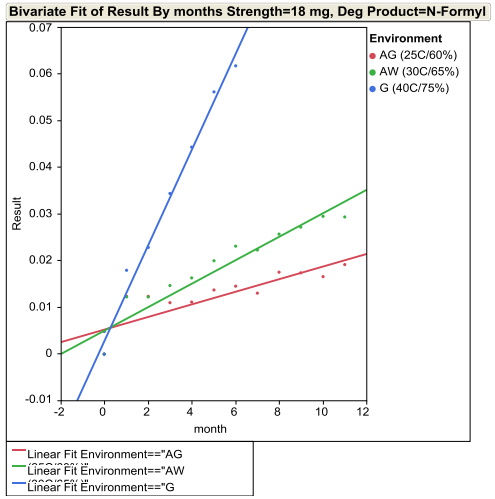
Deg A



6 mg, 3% dl, Deg A



18 mg, 9% dl, Deg A

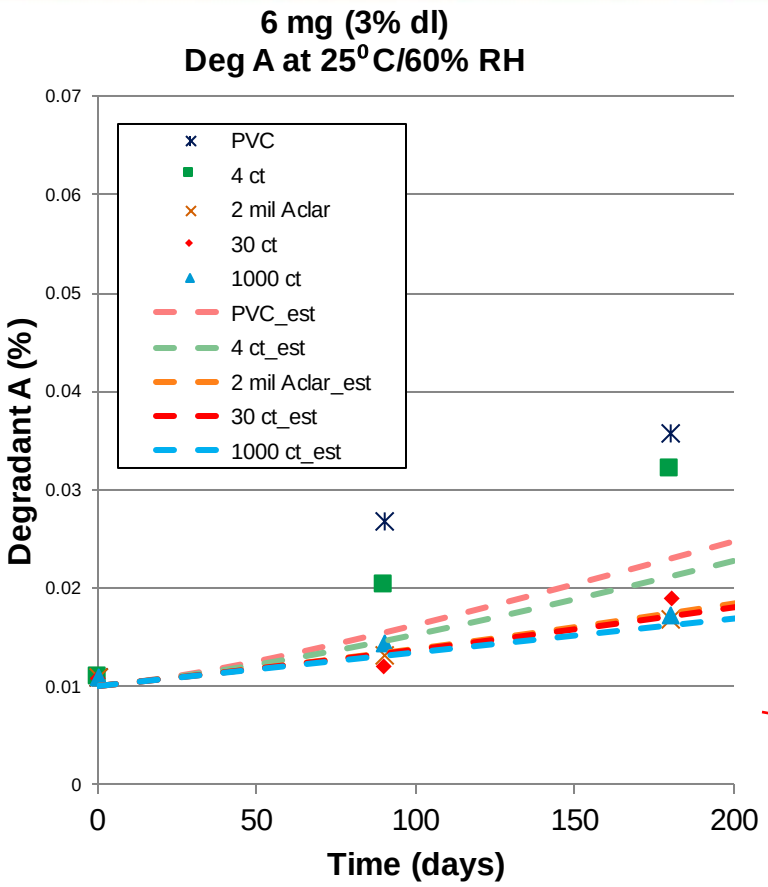


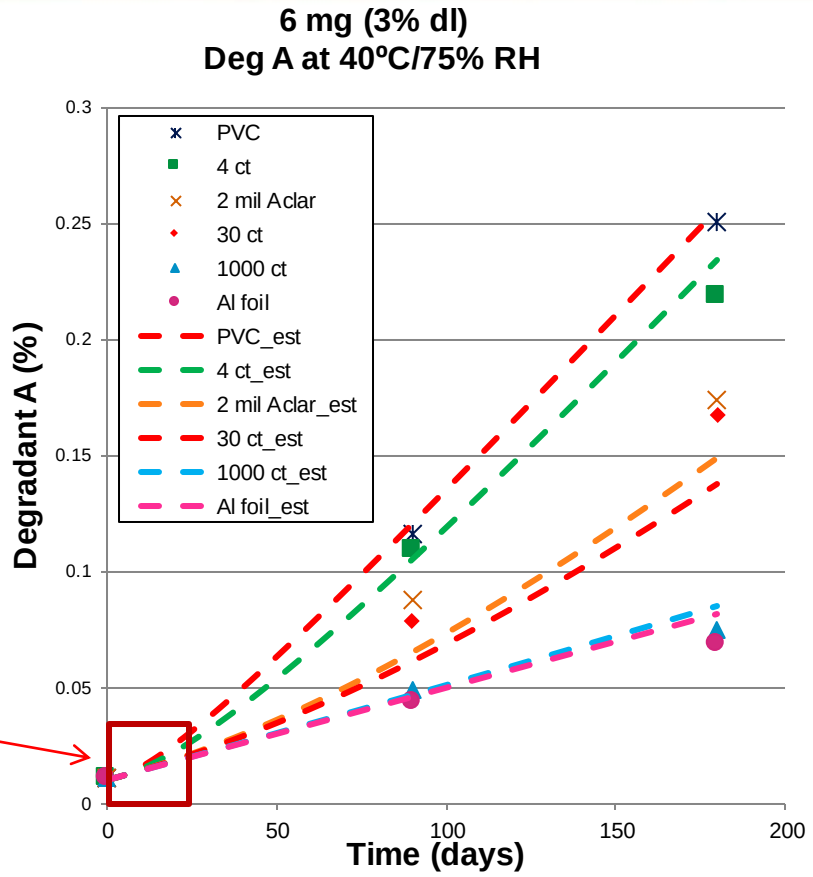
Note the low levels of degradation at the milder temperature/humidity conditions

Statistically modeled impact of measurement uncertainty

- Standard deviation of 10%
- 1000 simulated results for each regression fit
- Obtained parameter estimates and predicted monthly rate at 25ºC/60%RH (no package)

Case Study A Example Results: Combined with Package Modeling





- Package modeling using single ASAP coefficients (without simulated uncertainty) underestimates 6 mg tablet degradation in 4 ct bottle and PVC but shows better agreement for other package types for degradant A at 25 ^{0}C/60%RH. Note the low degradation levels
- Package modeling shows better agreement with all package types at 40 ^{0}C/75%RH where the degradation level is near the target utilized in the ASAP study design

Case Study A: Summary

- Traditional open dish data degradation rates for 6 and 18 mg tablets fall within the simulated uncertainty range (using 10% SD)
- Consistency in degradation rates is observed for dose strengths with the same drug load (tablets are just different size)
- Degradation levels at 25ºC/60% are low (not even above the reporting threshold of 0.05%) – very stable product
- Good agreement when combined with package modeling for most of the package configurations at 25ºC/60% and 40ºC/75% conditions
- Follow-up ASAP study under way with additional drug loads
  - Isoconversion target of 0.5% for all dose strengths
  - Low degradation rates will extend times even at elevated temperatures

Case Study B : Background

- Initial ASAP Study using standard protocol performed on 2.5 mg tablets (2.6% drug load) – not commercial image
- Primary degradant (Sulfoxide) specification = 1.0%
- Degradation level achieved using standard protocol ~0.4-0.6%
- Second round ASAP study performed using finalized commercial image tablets (2 drug loads 2.6% and 21%)
- Second round ASAP study performed on both drug loads to refine estimates and designed based on initial ASAP study data

Special Thanks to Jose Cintron, Chad Wolfe, and Henry Macler for providing Case Study B information

Case Study B : Refined ASAP Design

- Study Constraints: Maximum of 14 days; RH 10-75%; Temp 30-80 °C
- Target Degradation level of 1.0% Sulfoxide

High Drug Load

Temperature	RH	D-Optimal High Drug Load Days
70	70	11
70	75	8
75	55	13
80	45	12
80	75	3

Low Drug Load

Temperature	RH	D-Optimal Low Drug Load Days
55	75	14
60	75	7
75	65	2
80	30	14
80	55	2

High and Low Drug Load

	Temperature	RH	High Drug Load Days	Low Drug Load Days
	70	70	11	3
	70	75	8	2
	75	55	13	4
*	80	40	15	7
	80	75	3	1

*adjusted from high drug load due to chamber availability

Case Study B : Refined ASAP Study Results

Study Conditions and Results

Formulation	Target Days	Target Temp. (°C)	Actual Temp. (°C)	Target RH	Actual RH	Sulfoxide (NMT 1.0%)	
21% Drug Load (20 mg Tablet) *	0	-	-	-	-	0.0614	
	11	70	70	70	70	0.4650	
	8	70	70	75	74	0.4641	
	13	75	75	55	55	0.3090	
	15	80	79	40	42	0.3758	
	3	80	79	75	79	0.5279	
2.6% Drug Load (5 mg Tablet)	0	-	-	-	-	0.0832	
	3	70	70	70	70	0.9855	
	2	70	70	75	74	0.9308	
	4	75	75	55	55	0.8573	
	7	80	79	40	42	0.4724	**
	1	80	79	75	79	1.6792	***

*High drug load formulation did not achieve the desired isoconversion degradation level of 1.0% - ranged from ~0.31 to 0.53% degradation

**Isoconversion target not achieved

***Sticking of tablets and higher than expected degradation level observed - possible failure mode (Form/Phase transition, melt) may have affected the reaction kinetics leading to higher levels of degradation

Case Study B : Refined ASAP Study Results

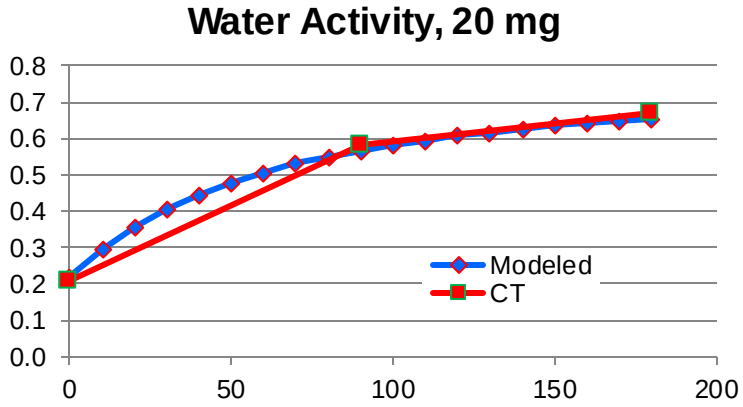
Model Coefficients

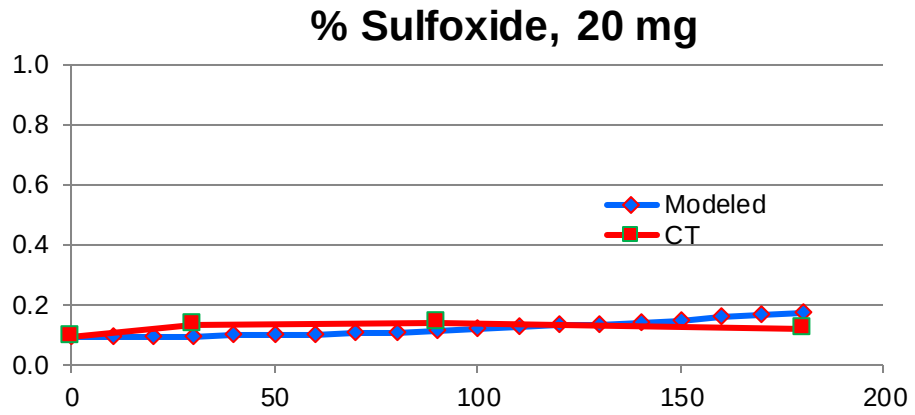
Formulation	Degradant	Intercept (Monthly Rate)	Coefficient for 1/T	Ea (kcal/mol)	Coefficient for RH (B Term)
21% Drug Load (20 mg Tablet)	Sulfoxide	32.8416	-12649.5	25.1	0.059
2.6% Drug Load (5 mg Tablet)	Sulfoxide	28.5965	-11091.9	22.0	0.086

- High B term for the 2.6% DL strongly influenced by the high level of degradation observed for the 79% RH/79°C condition

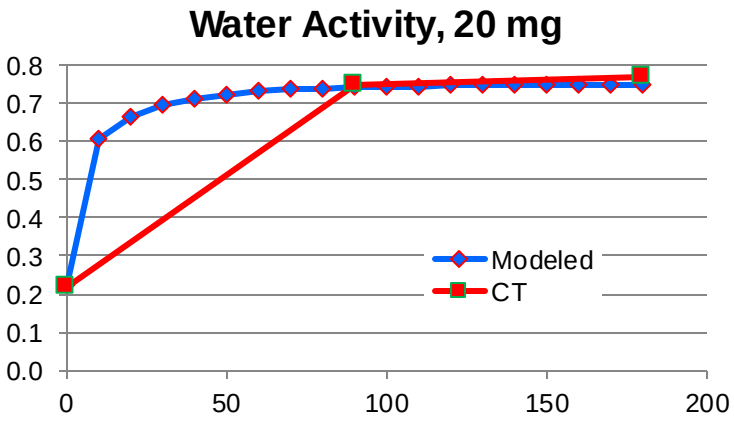
- When combined with package modeling, predictions comparing limited clinical trial stability data at the 40ºC/75%RH accelerated condition show good agreement for the 21% drug load.

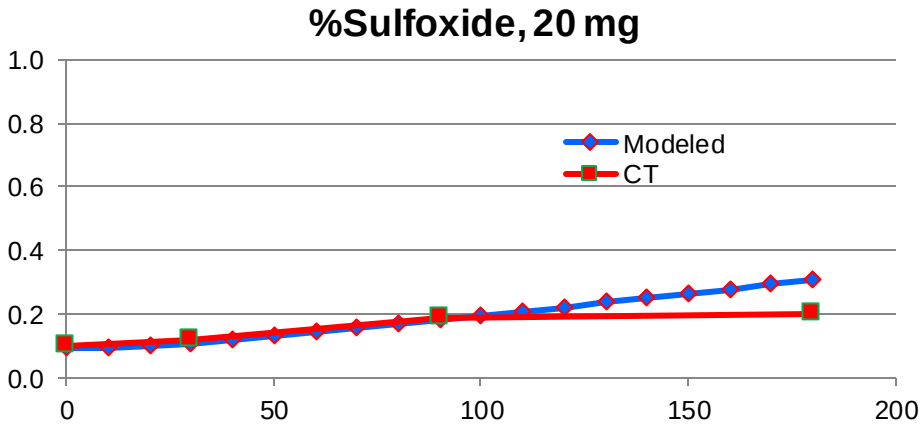
Case Study B Example Results: Combined with Package Modeling





21% DL PREDICTED VS ACTUAL - 2 MIL Aclar® at 40ºC/75%RH





21% DL PREDICTED VS ACTUAL – 7 CT HDPE BOTTLE at 40ºC/75%RH

Case Study B : Next Steps -Refined Study Plan

•Study Constraints: 30-75 °C; 10-75% RH; Maximum 5 weeks for high DL and 2 weeks for low DL

•Maximum temperature and humidity conditions were restricted to 75 °C and 75% RH in order to avoid possible failure modes (eg. Form/Phase transition, melts, …observation of sticking tablets in the low DL)

•Target Degradation level of 1.0% Sulfoxide for the high DL

High DL Study Conditions

Temp. (°C)	RH	Days
65	75	34
70	70	26
70	75	20
75	60	28
75	75	11

Low DL Study Conditions

Temp. (°C)	RH	Days
50	75	14
65	75	3
70	55	10
75	50	10
75	65	3

Low DL Study If Using the High DL Conditions

Temp. (°C)	RH	Days
65	75	3
70	70	3
70	75	2
75	60	4
75	75	1

• Study in progress

Continuous Improvement – How Lilly is Improving the Program

- ASAP Working Group Construct
  - Seek interest and build expertise across specialty areas

  (cross-functional Subject Matter Experts)
    - Analytical
    - Stats
    - Formulation
    - Packaging
    - Preformulation
  - Assess implementation and impact of using ASAP to portfolio
  - Share case studies and learning (results, predictions, etc.)
  - Improving processes, tools (including software purchase), and study execution
  - Can help leverage getting needed resources for studies to intentionally explore failure modes

Process Improvements

- Improve study execution concepts
  - Focus on isoconversion and degradant(s) that drive the degradation product control strategy
- Increased capacity
  - Additional ovens/incubators
- Understanding Equilibration and Failure Mode Questions
  - How do we know that coated tablets have equilibrated to the incubator conditions? Pre-equilibration at ambient temperature? Do we accept? Closed versus open systems?
  - Best practices to understand potential failure modes to inform study design –what questions do we ask up front?

ASAPprime™ Software

- Commercially available validated statistical modeling software based on the ASAP paradigm
- Developed by Ken Waterman who pioneered this approach at Pfizer and founded FreeThink Technologies Inc.
- Analyzes the effects of temperature and relative humidity on product stability
- Performs Monte-Carlo simulations to estimate confidence intervals for a projected shelf-life under various storage conditions
- The software nicely integrates product and packaging modeling components

http://freethinktech.com/

Summary

- Historical approach
  - Fixed time points for all accelerated conditions that are not necessarily designed to give equal amounts of degradation (isoconversion)
  - Extrapolation to real time conditions is often limited
  - Package selection requires package screening studies with at least 6 months of stability data
- ASAP approach
  - Scientifically selected accelerated conditions targeting the same amount of degradation for each condition (isoconversion)
  - Extrapolation to real time conditions is often very good
  - Package selection can be determined through the combination of the product degradation kinetics (ASAP) and package modeling, eliminating the need of package screening studies
  - Can help guide the control strategy (e.g. initial water activity limits, packaging configurations, Genotoxic Impurity Strategy)

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See additional references at http://freethinktech.com/resources.html

Questions?