Predicting the Long-Term Stability of Solid-State Pharmaceuticals

ASAP (Accelerated Stability Assessment Program): Theory, Limitations and Applications

London, March 2015

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Environmental Factors that Influence the rate of chemical degradation in the solid state

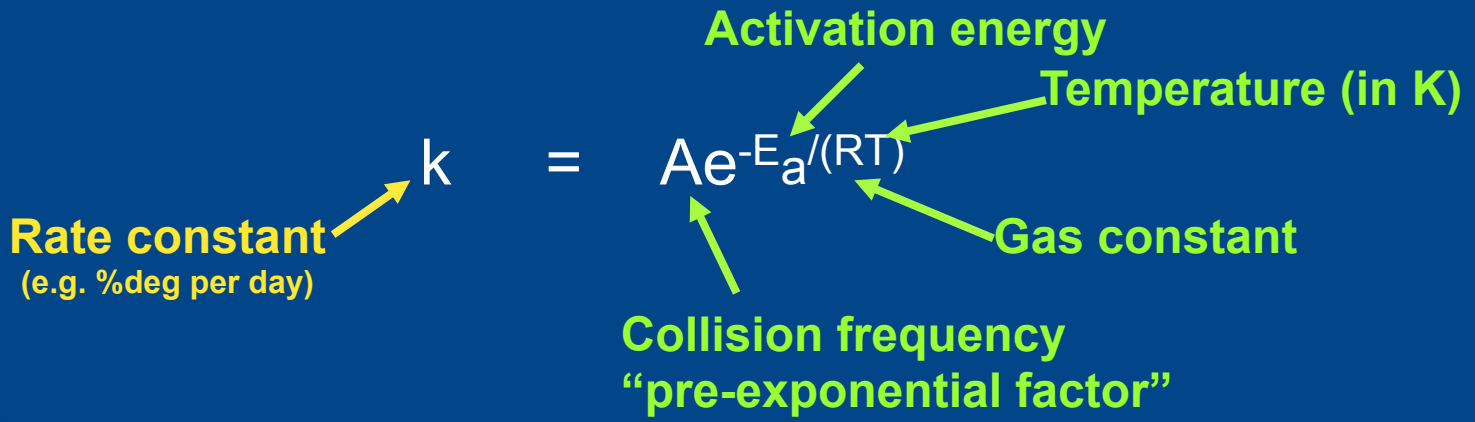
1. Temperature
2. Humidity
3. Light
   - Accepted rapid ICH accelerated conditions exist
   - Packaging used for most solid drug products protect from light
4. Oxygen level

(etc.?)

Not in scope of presentation

Temperature and Humidity…

- Schumacher (1972) and Grimm (1986, 1998) proposed four long-term stability storage conditions
  - Zone 1: “Temperate” 21°C/45%RH
  - Zone 2: “Subtropical and Mediterranean” 25°C/60%RH
  - Zone 3: “Hot and Dry” 30°C/35%RH
  - Zone 4: “Hot and Humid” 30°C/70%RH
- Temperature, Arrhenius equation (ca. 1889):



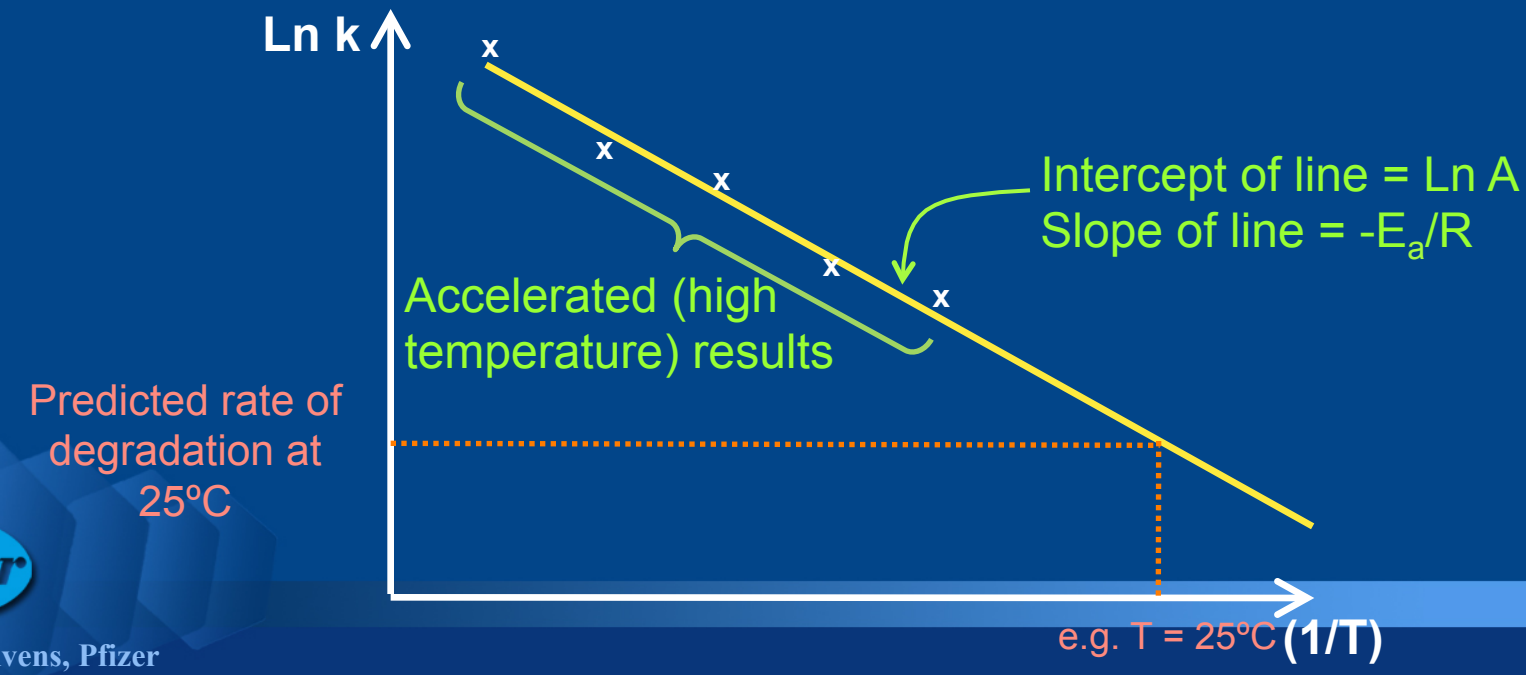
$$\ln k = \ln A - E_a/(RT)$$

Until recently only thought to apply ‘in general terms’ to solid-state pharmaceutical systems

Arrhenius Plots

The rate of a chemical reaction at a particular temperature can be interpolated / extrapolated from the rates at other temperatures

$$\text{Ln } k = \text{Ln } A - (E_a/R).(1/T)$$



Accurate application of Arrhenius to the solid state

Ken Waterman et.al.[1] cites two main reasons that led to the historical misconception that Arrhenius does not apply accurately to solid-state pharmaceuticals:

a) API is in multiple different micro-environments in solid state

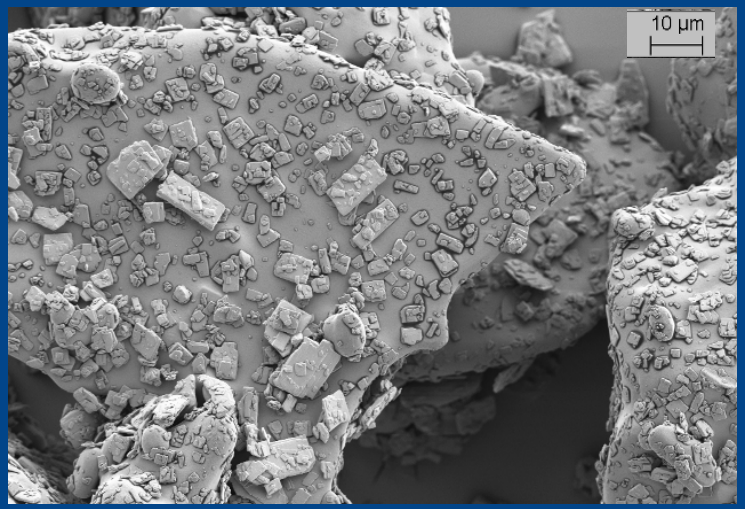
   (This can lead degradation curves that cannot be defined as simply 0^{th}, 1^{st} or 2^{nd} order curves - which can lead to errors in defining a reliable rate constant for chemical degradation)

b) Effect of relative humidity is not factored into the Arrhenius equation[2]

1. Waterman, K.C.; Carella, A.J.; Gumkowski, M.J.; Lukulay, P.; MacDonald, B.C.; Roy, M.C.; Shamblin, S.L. Improved protocol and data analysis for accelerated shelf-life estimation of solid dosage forms. Pharmaceutical Research 24 (2007) 780-790.
2. Actually back in 1977, a paper by Genton and Kesselring covered some of the ground *J.Pharm Sci* 66: 676–680 (1977)

API Micro-Environments in Solid-State

- Solution:
  - Molecules are in same environment
  - Reactivity shows homogeneous kinetics
- Solid State:
  - Molecules in different microenvironments:
    - crystal lattice
    - surface
    - amorphous
    - solid-solution
  - Multiple k's
  - Heterogeneous kinetics – formation of product is a superposition of multiple rates

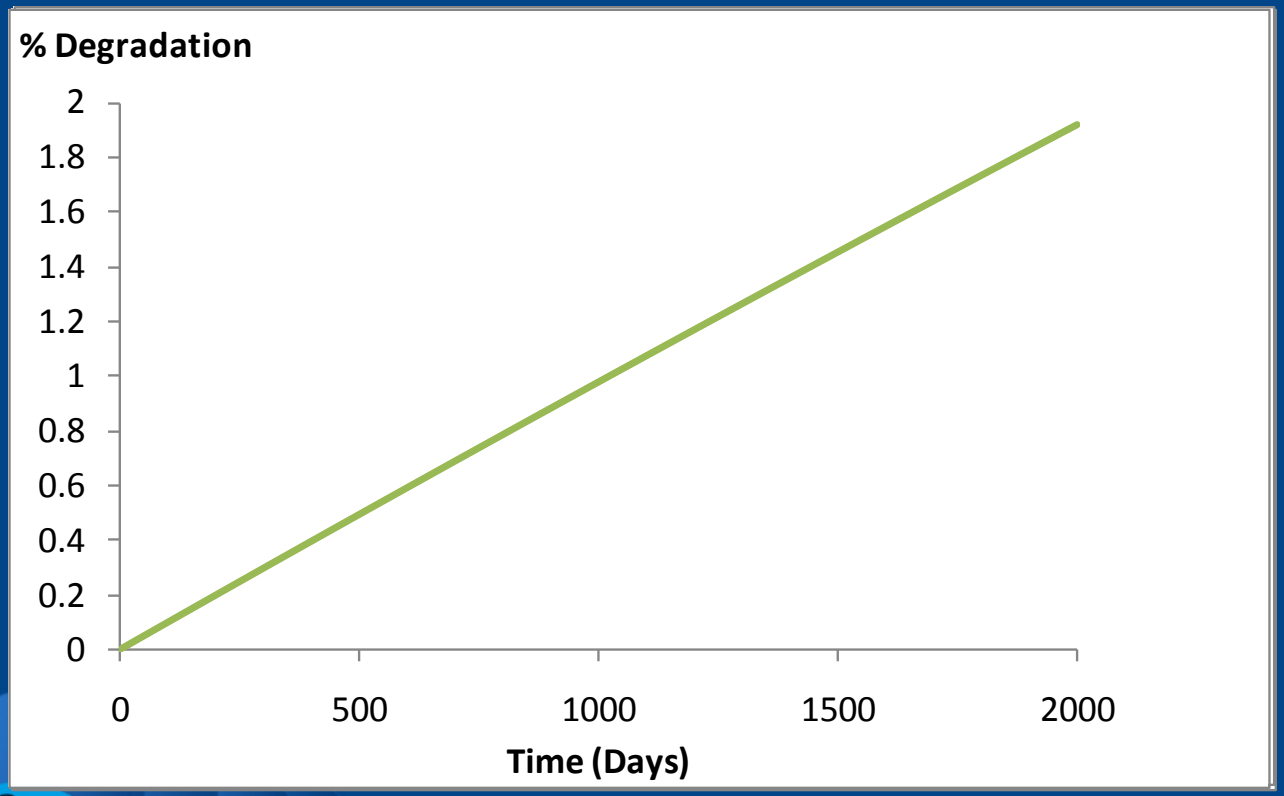


$$[P_t] = \Sigma_i k_i t$$ (different k for each API state)

  - Shape of degradation curve in solid state may not be well described by simple 0^{th}, 1^{st} or 2^{nd} order kinetics

Degradation Curves

Zero Order **First Order** **Second Order**

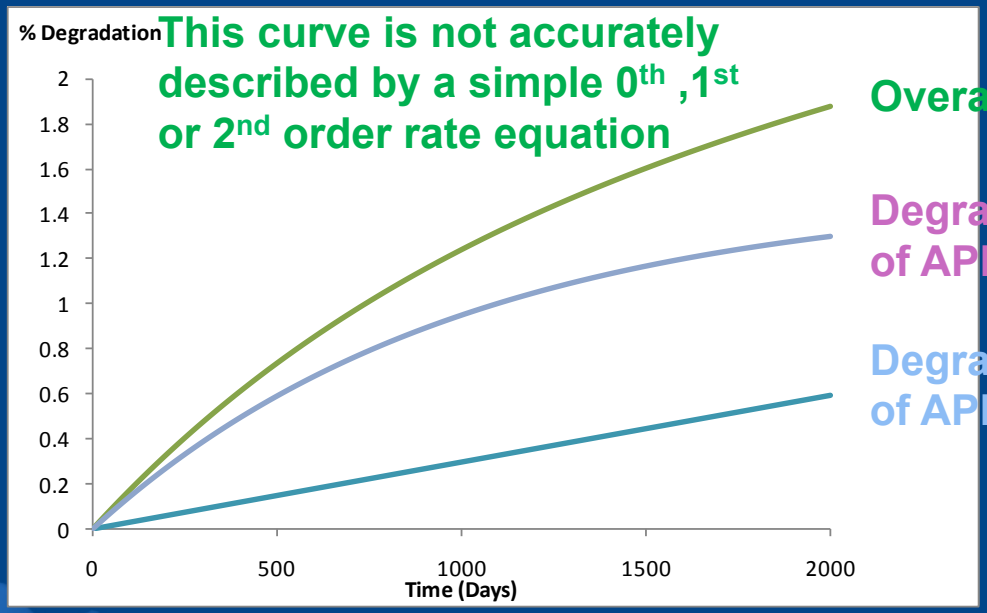


All curves appear linear over the first few % of degradation…

…if all API molecules are in same environment

Real-world Solid-State Degradation Curves

- ~50% (in our experience) appear to be essentially linear
- ~50% exhibit a degree of curvature



- Other causes of curvature are discussed later….

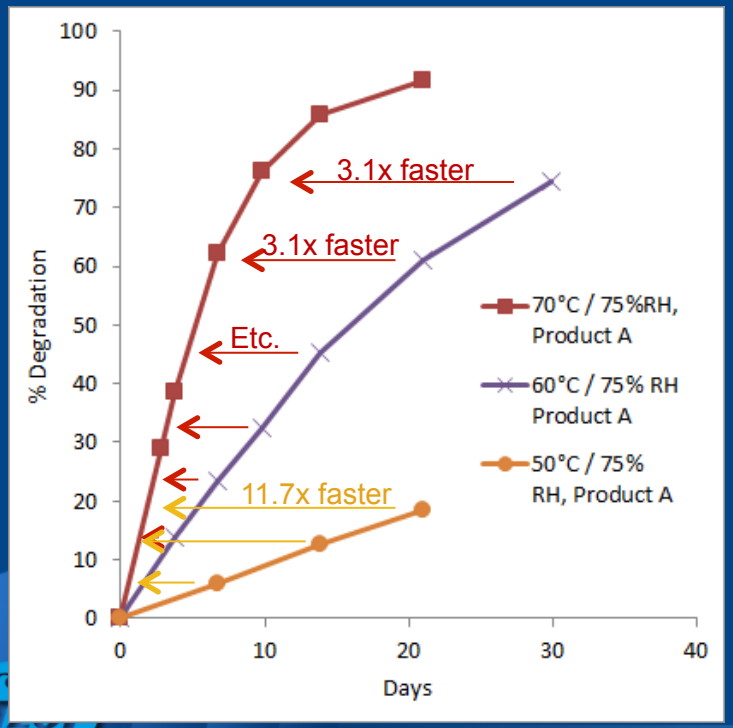
Dealing with real-world solid-state degradation curves

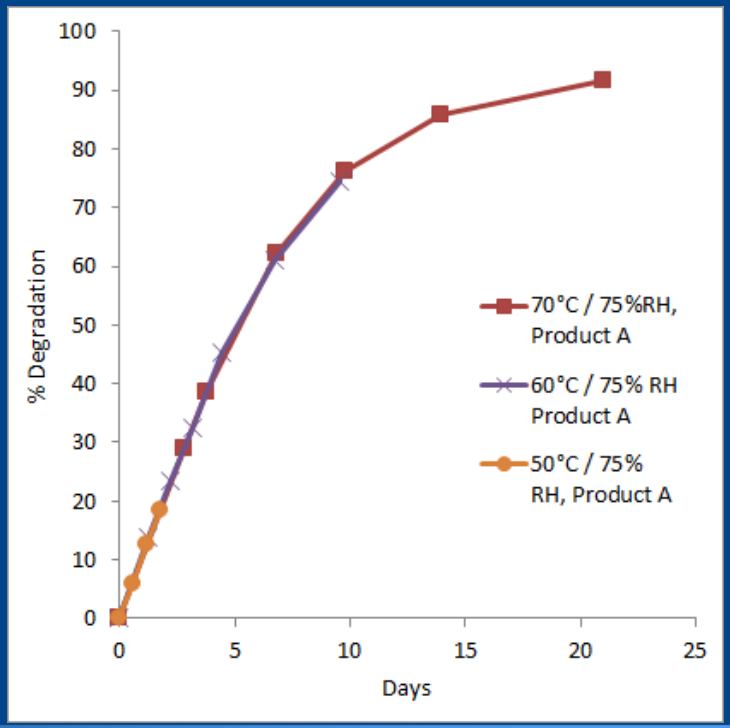
- Objective: to calculate ‘k’ (rate constant for the degradation) over a range of temperatures so that an Arrhenius plot can be produced
- Problem…in order to calculate k, we need to apply a model to account for the curvature of degradation
- Plan A: acquire %deg results at multiple timepoints so that a empirical model can be applied to the data (→ k)
  - Labour intensive
  - Prone to errors associated with fitting models to data (>1 parameter is required to model the data)
- Plan B: use a ‘Time to failure’ or ‘Isoconversion’ approach

Degradation Kinetics at Different Conditions

For a given system, the *shape* of the curve (i.e. degradation kinetics) is usually very similar across different stability conditions, just the timescale is different

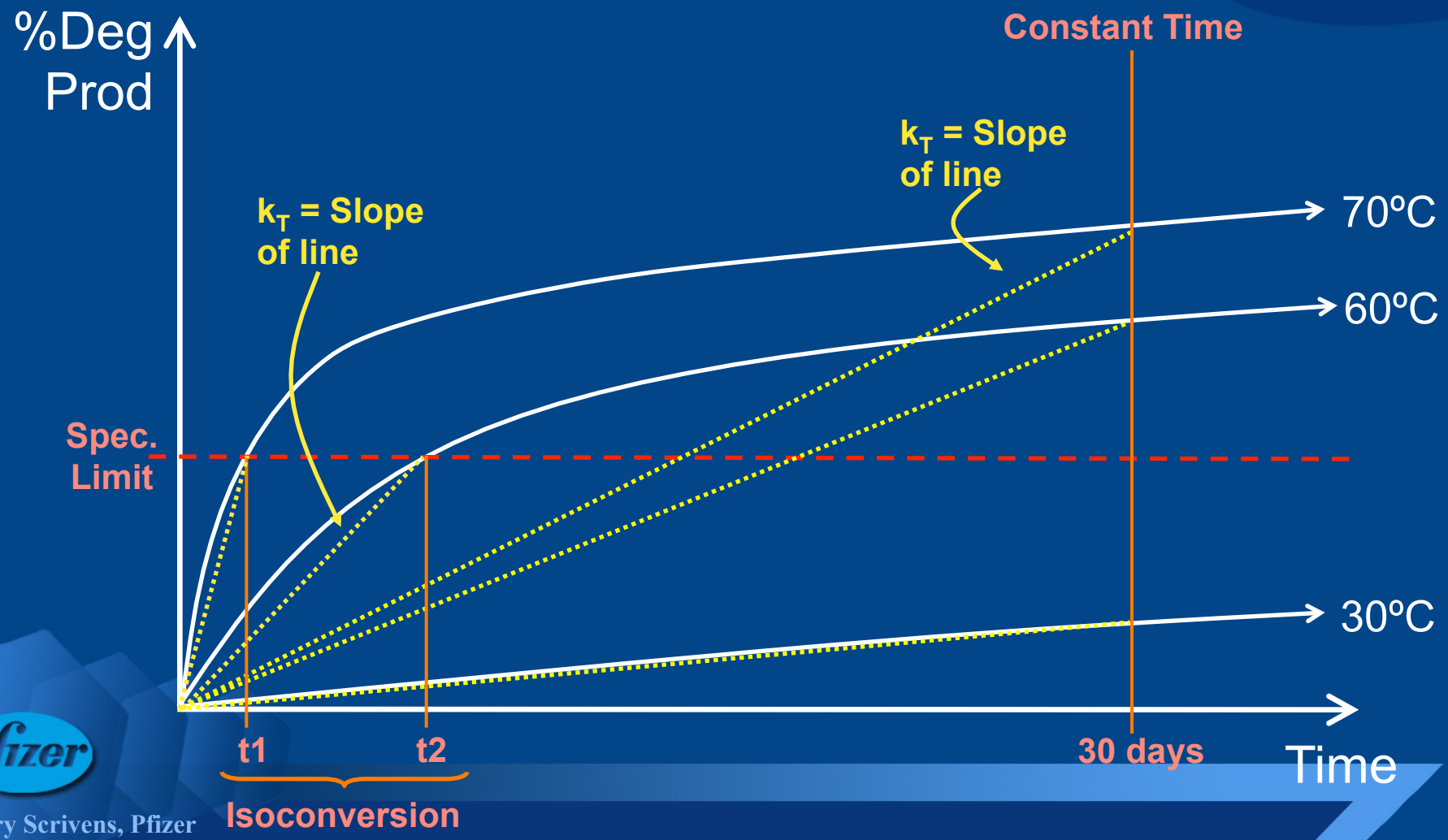
(cases where this assumption is invalid are discussed later)





Traditional (Constant Time) Approach vs. Isoconversion Approach

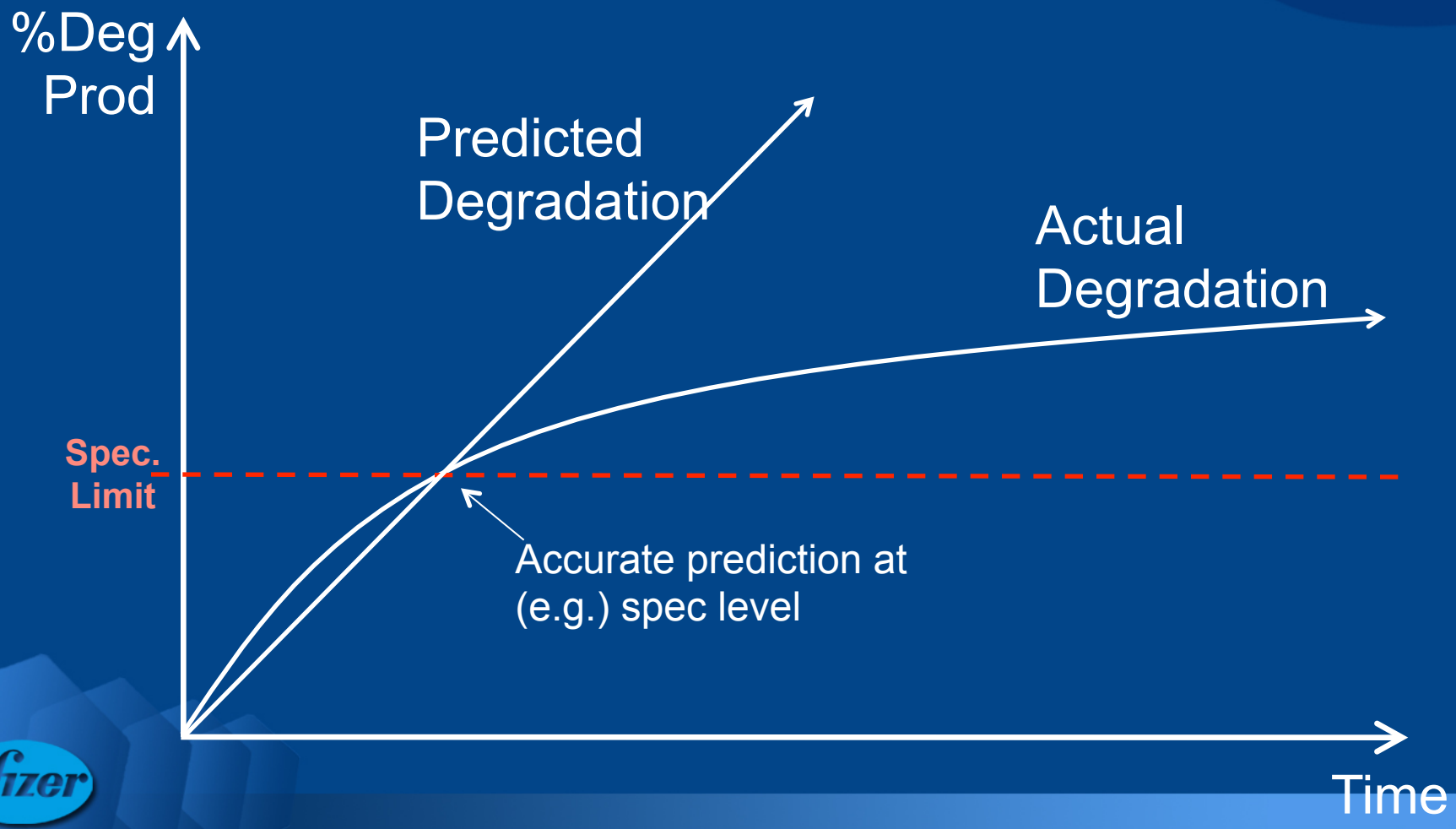
With an isoconversion approach, the shape of the degradation curve is unimportant



Isoconversion Principle - Summary

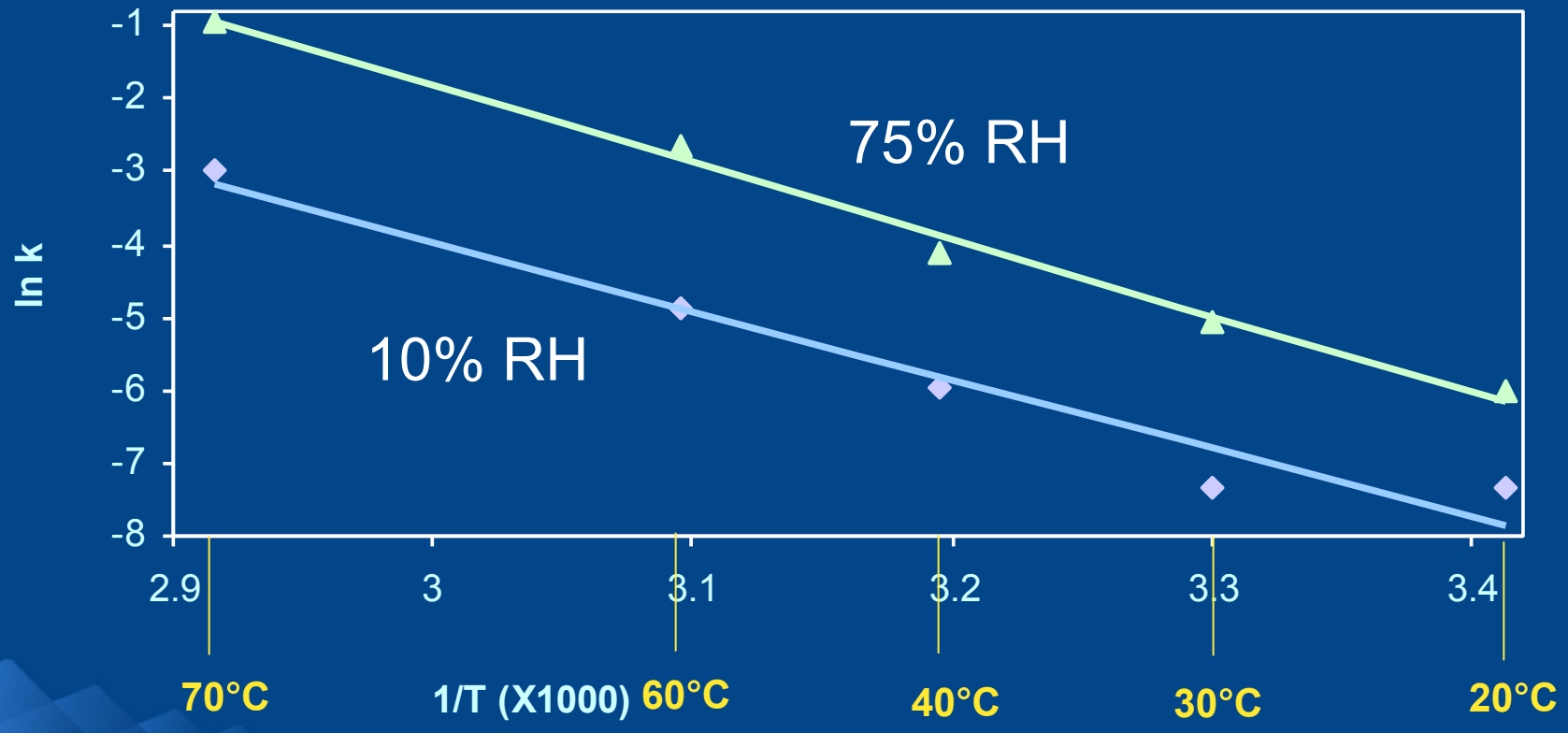
- Select timepoints for each Temp / %RH condition to give approximately the level of degradation that you're interested in (typically the **specification limit)**
  - Shape of the degradation curve (order of reaction) is unimportant
  - Degradation far removed from specification level may lead to an inaccurate shelf life prediction
  - Proportion of reaction from different API environments assumed to be consistent across different conditions

Caution: Isoconversion Approaches



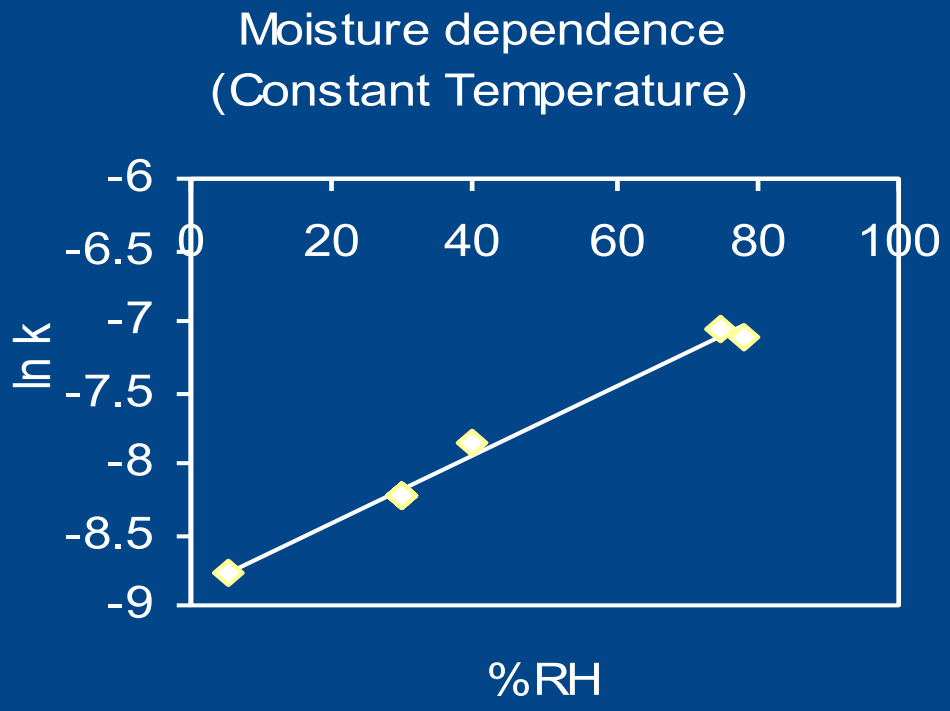
Applying Arrhenius to the Solid State: 2. Effect of Relative Humidity

Degradation of Aspirin Tablets:



Humidity Sensitivity

- Observation: solid-state degradation rates increase exponentially with %RH



- At constant temp, ln k = B(%RH)

Humidity Corrected Arrhenius Equation

Selected by user, at least 3 combinations required

$$\ln k = \ln A - E_a/(RT) + B(\%RH)$$

3 parameters need to be determined (using multilinear regression) for each degradation reaction

Measured (calculated from %degradation results)

Accelerated Stability Protocol Design

- Isoconversion: aim to degrade sample to the specification level for all conditions
  - Initial trials: use average (typical) Ln A, E_a and B values
  - Subsequent trials on same drug product / API can use Ln A, E_a and B values from previous studies to provide better isoconversion (an iterative process)
- A minimum of 3 different temperature - %RH combinations are required (3 unknown parameters, Ln A, E_a and B to be determined)
  - More than 3 conditions are required in order to provide greater confidence in prediction and to provide some measure of goodness of fit to ASAP model (an 'over-determined' system)

Standard (Default) ASAP Protocol*

Conditions and durations chosen for their practicality and to provide about 0.5% degradation based on typical Ln A, E_a and B values

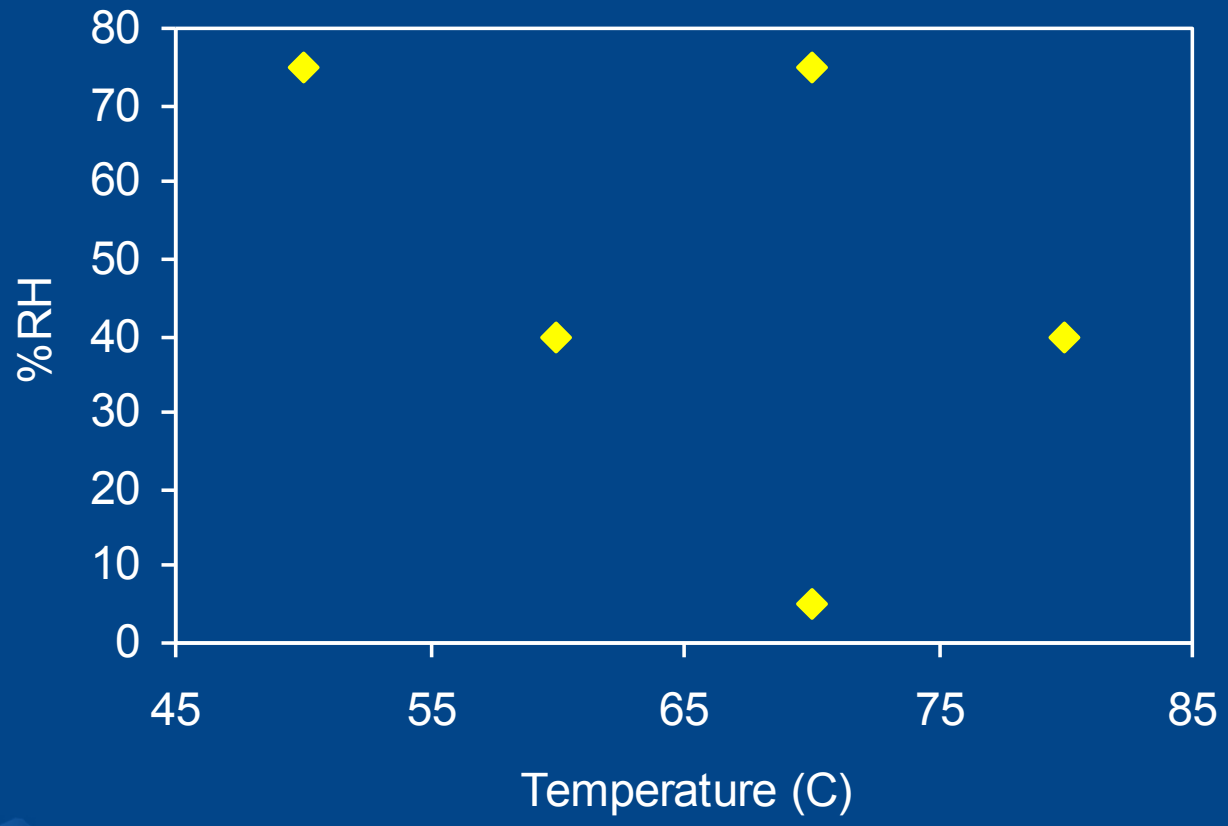
Protocol	T (°C)	%RH	Days
API Stability	70	5	14
	70	75	14
	80	5	14
	80	40	14
Drug Product Stability	50	75	14
	60	40	14
	70	5	14
	70	75	1
	80	40	2

*Other temperature / humidity / duration combinations can be used to meet the needs of the particular application

Protocol Design: Practicalities

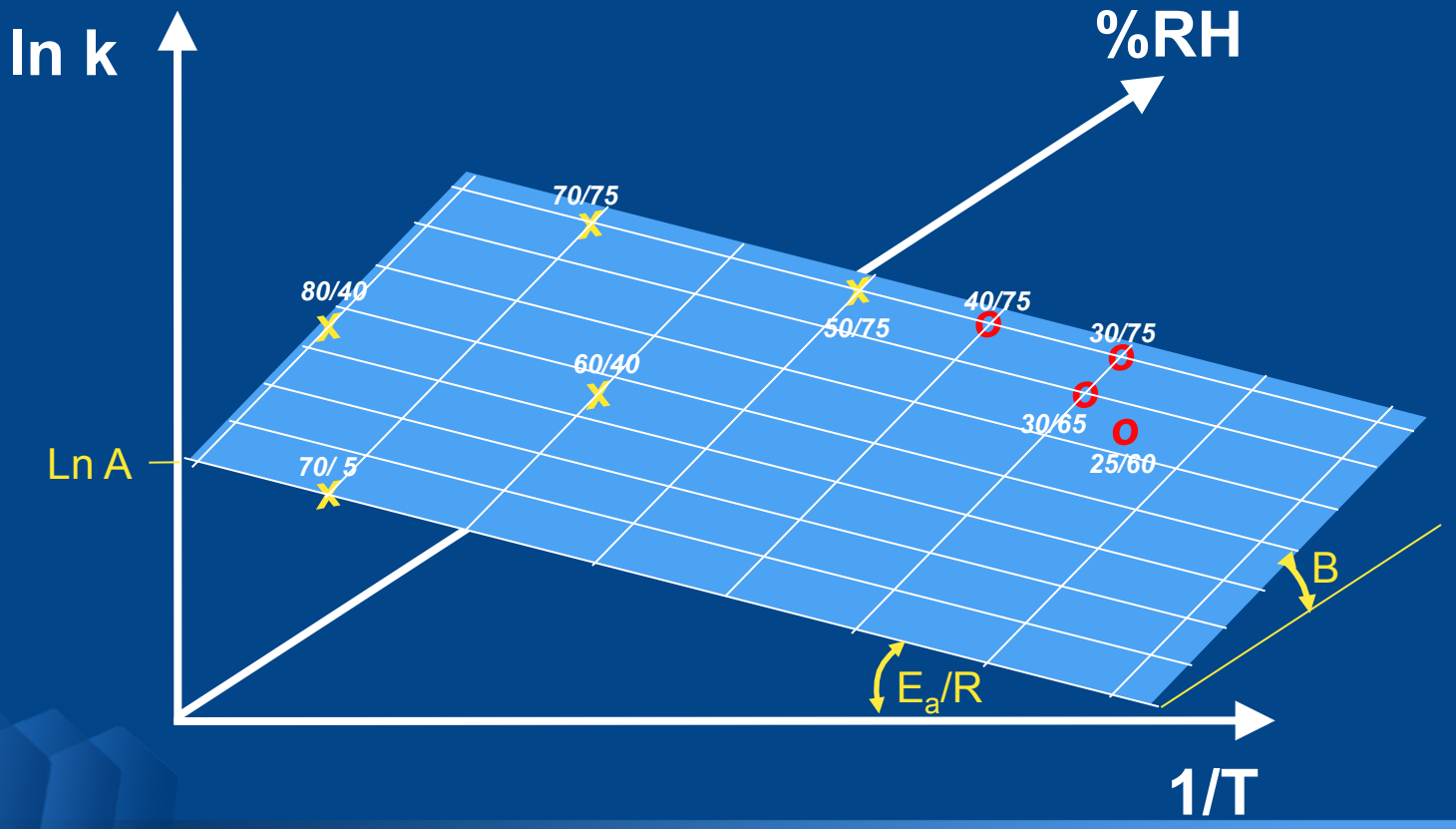
- Humidity-controlled ovens
- Saturated Salt Solutions, e.g.:
  - 30%RH: $MgCl_2$
  - 50%RH: NaBr
  - Etc.
- Amebis

ASAP Drug Product Design Space (DOE)



Visualizing the ASAP Experiment

$$\ln k = \ln A - E_a/R(1/T) + B(\%RH)$$



Interpretation of E_a and B Values: Quantifying the effect of temperature and %RH

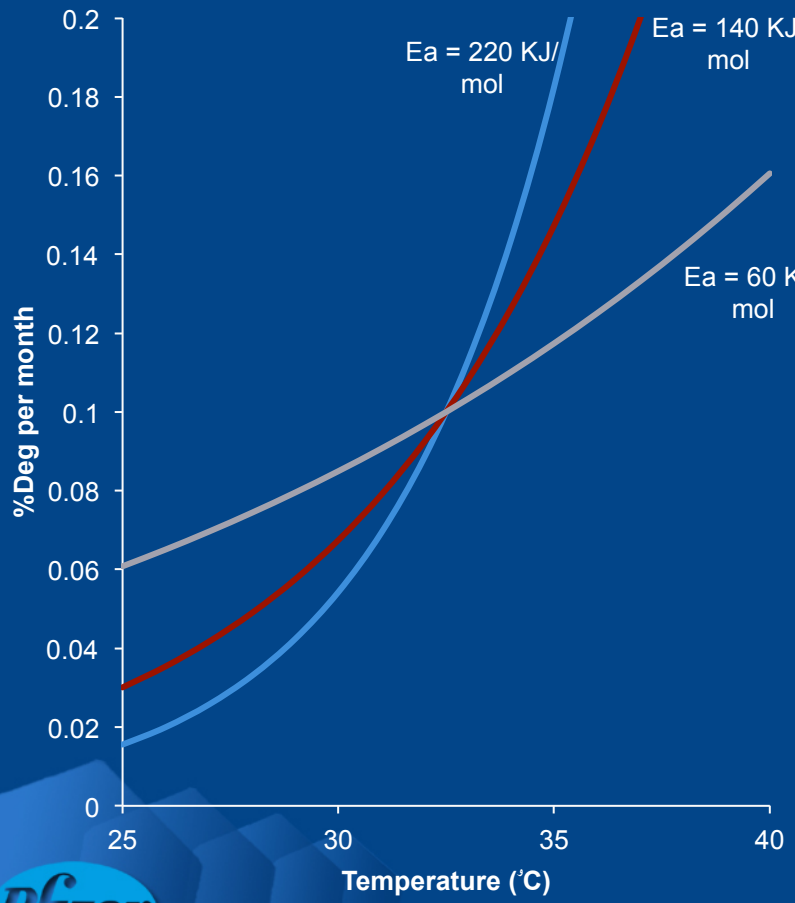
E_a Term: a measure of the temperature dependence of the degradation

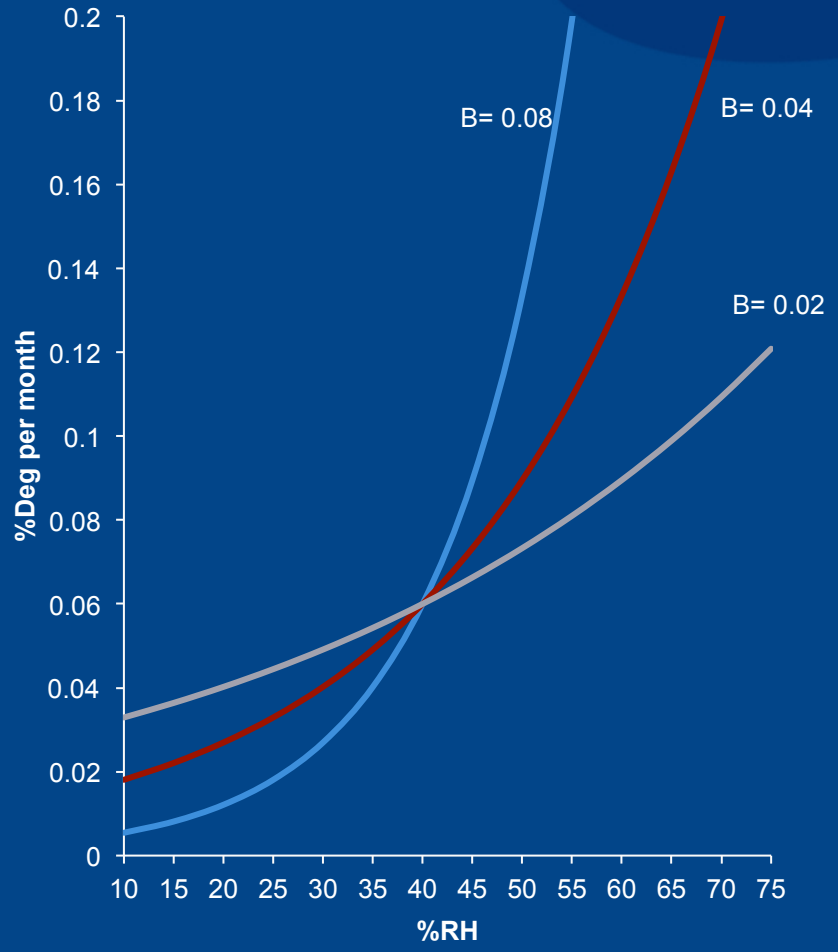
E_a = 50 KJ.mol^{-1}, degradation rate 1.9x between 30ºC and 40ºC
E_a = 100 KJ.mol^{-1}, degradation rate 3.6x between 30ºC and 40ºC
E_a = 150 KJ.mol^{-1}, degradation rate 6.7x between 30ºC and 40ºC

B Term: a measure of the moisture dependence of the degradation

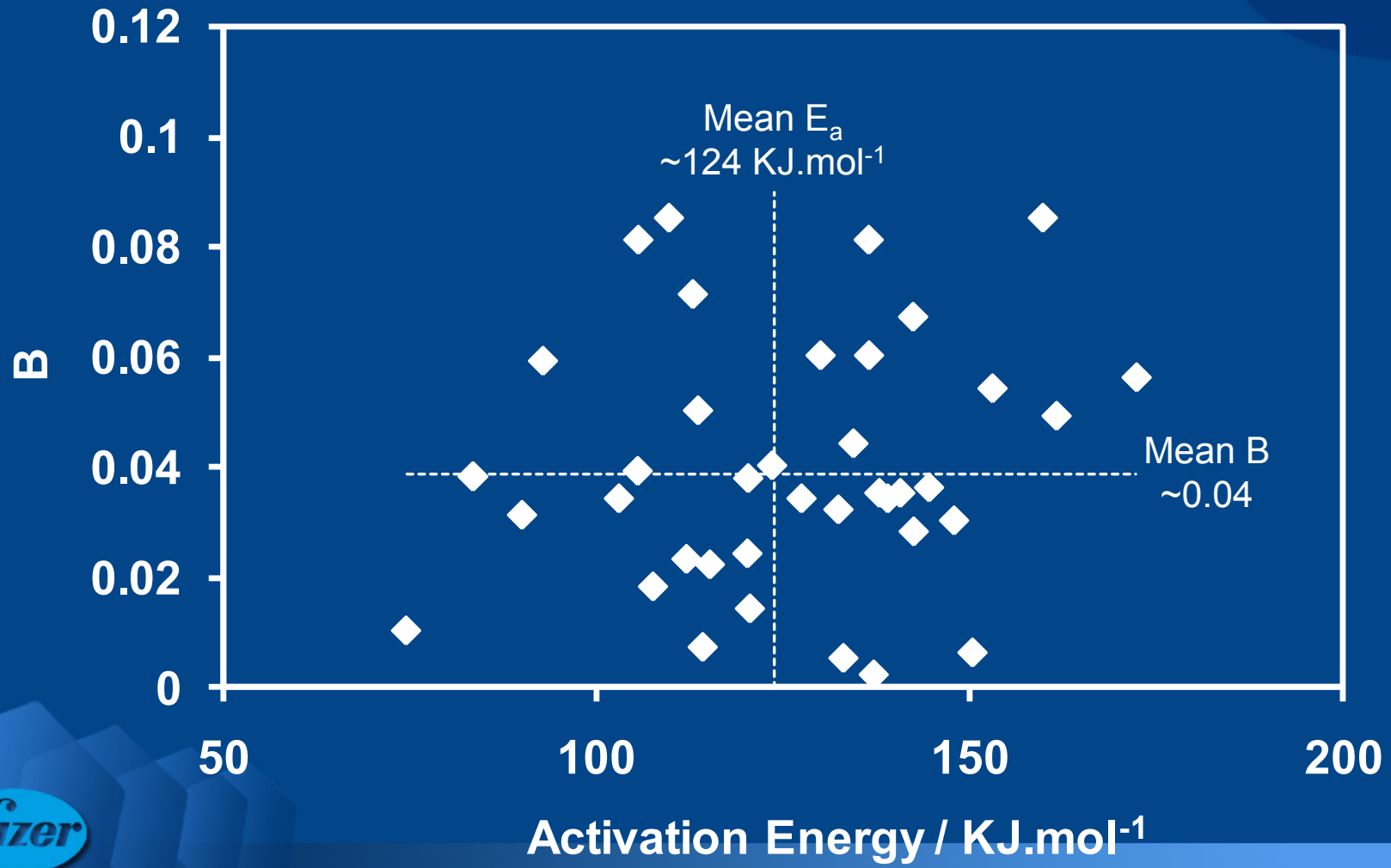
B = 0.07, degradation rate doubles for every 10% RH increase
B = 0.035, degradation rate doubles for every 20% RH increase

Using E_a and B to Quantify the effects of Temperature and %RH…Examples



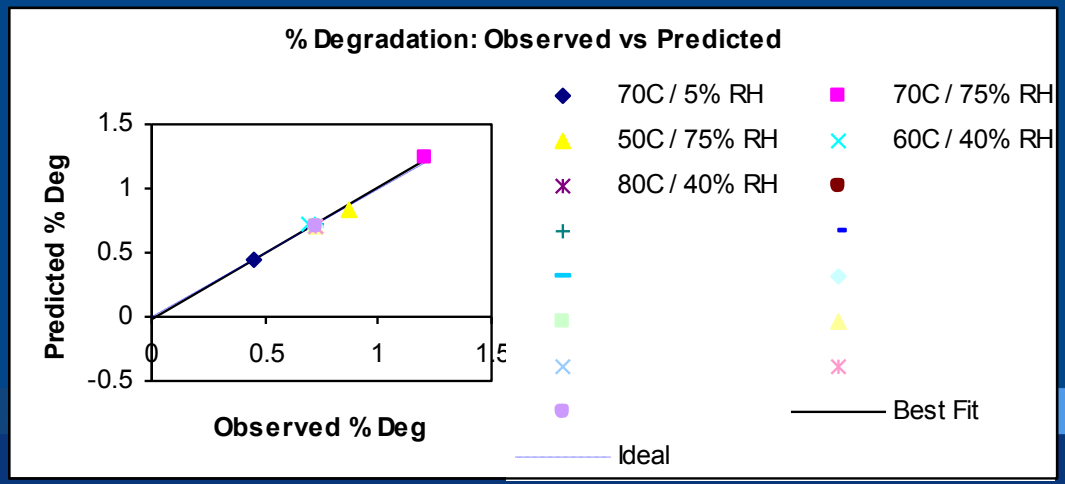


Typical E_a and B values (n=60)



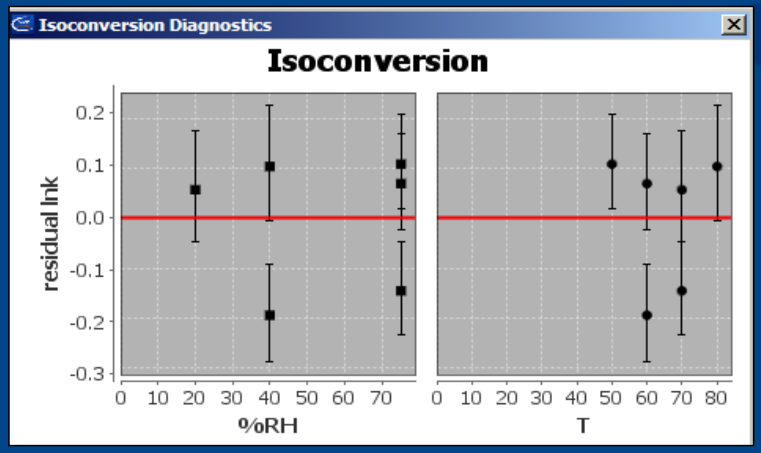
Checking the Goodness of Fit of data to the ASAP Model

- Comparison of prediction against actual long-term stability is of course the 'definitive-test' of the ASAP approach
  - Many examples of excellent predictions on historical batches (retrospective analysis)
- How can we assure ourselves that the ASAP approach will work on new products in development (without waiting 2 years to find out)?
  - Internal validation of model: ability to predict 'itself' – e.g. use 4 of the ASAP conditions to predict the 5th; evaluating how well data fit the model

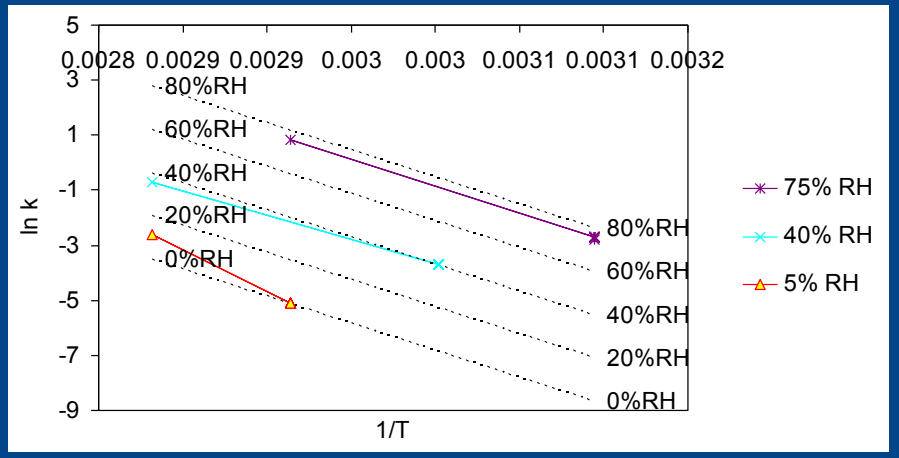


Checking the Goodness of Fit of data to the ASAP Model

- Examination of residuals:



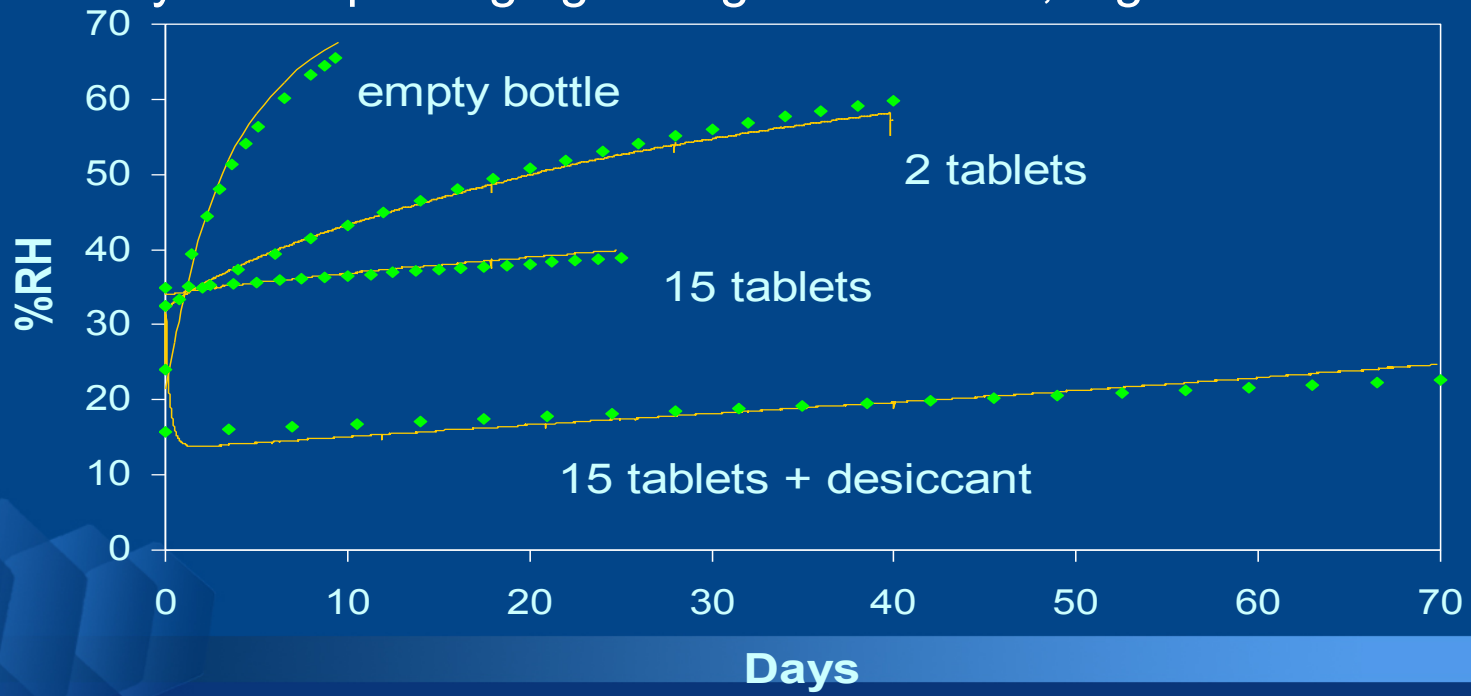
- Examination of Arrhenius Plots:



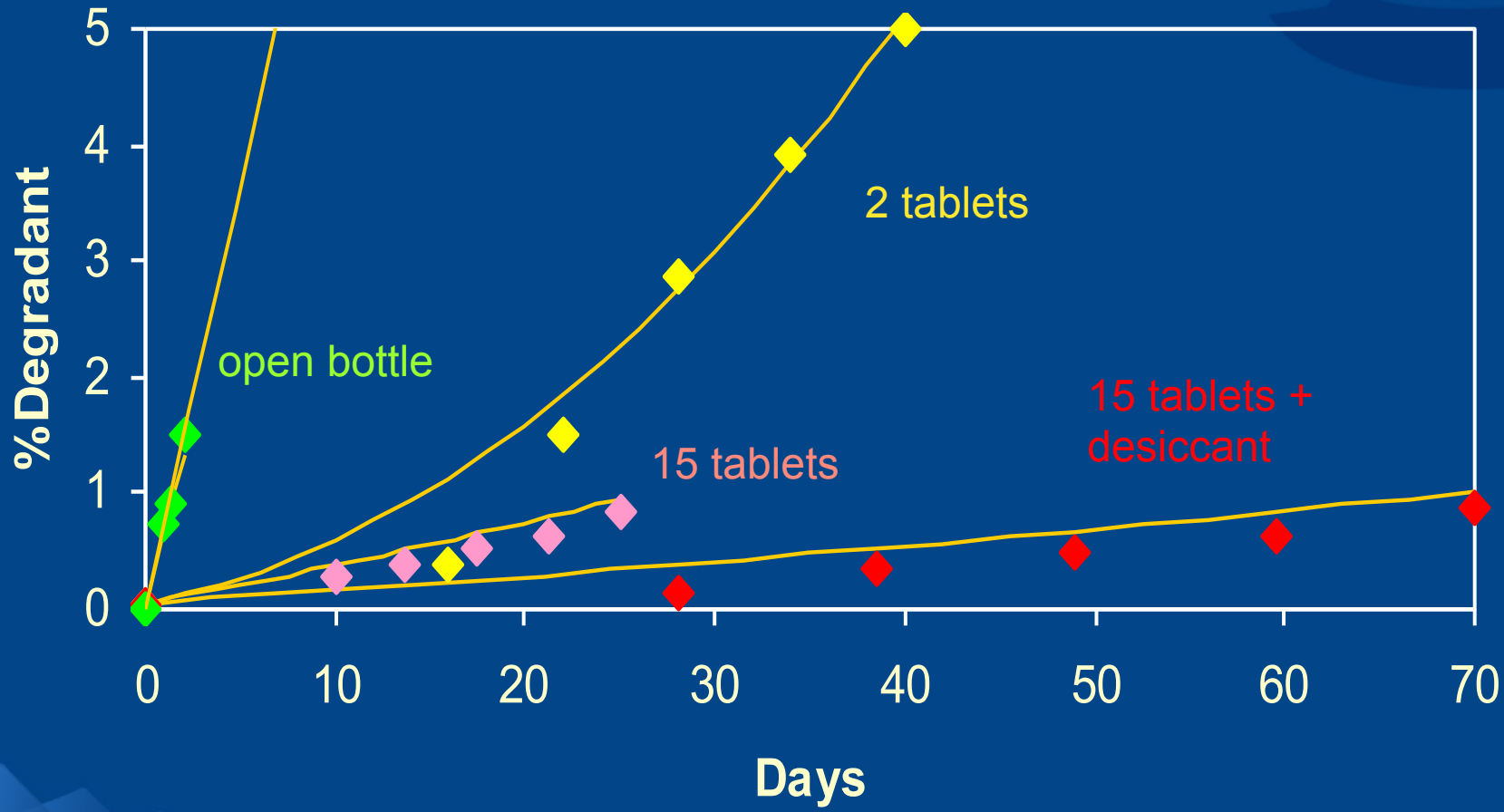
- $R^2_{prediction}$

Estimation of Shelf-Life for Packaged Products

- Ln A, E_a and B terms can be used to predict the rate of degradation: just need to know temperature and humidity
- But the *humidity inside the packaging* needs to be known for accurate packaged product stability predictions
  - Humidity inside packaging changes over time, e.g.:



Predicted (lines) vs. Measured Degradation



Drug Product 'A' in 60-cc HDPE Bottles (40°C/75%RH)

The humidity inside the packaging can be accurately predicted

- In order to do this you need to know:
  1. The 'MVTR' (moisture vapour transmission rate) of the packaging, and
  2. The Moisture vapour sorption isotherm for your product (can be obtained by combining the isotherms for the individual excipients of the product) and the desiccant (if using)
  3. The ingoing water content / water activity of the tablets (& desiccants)

See Next Presentation

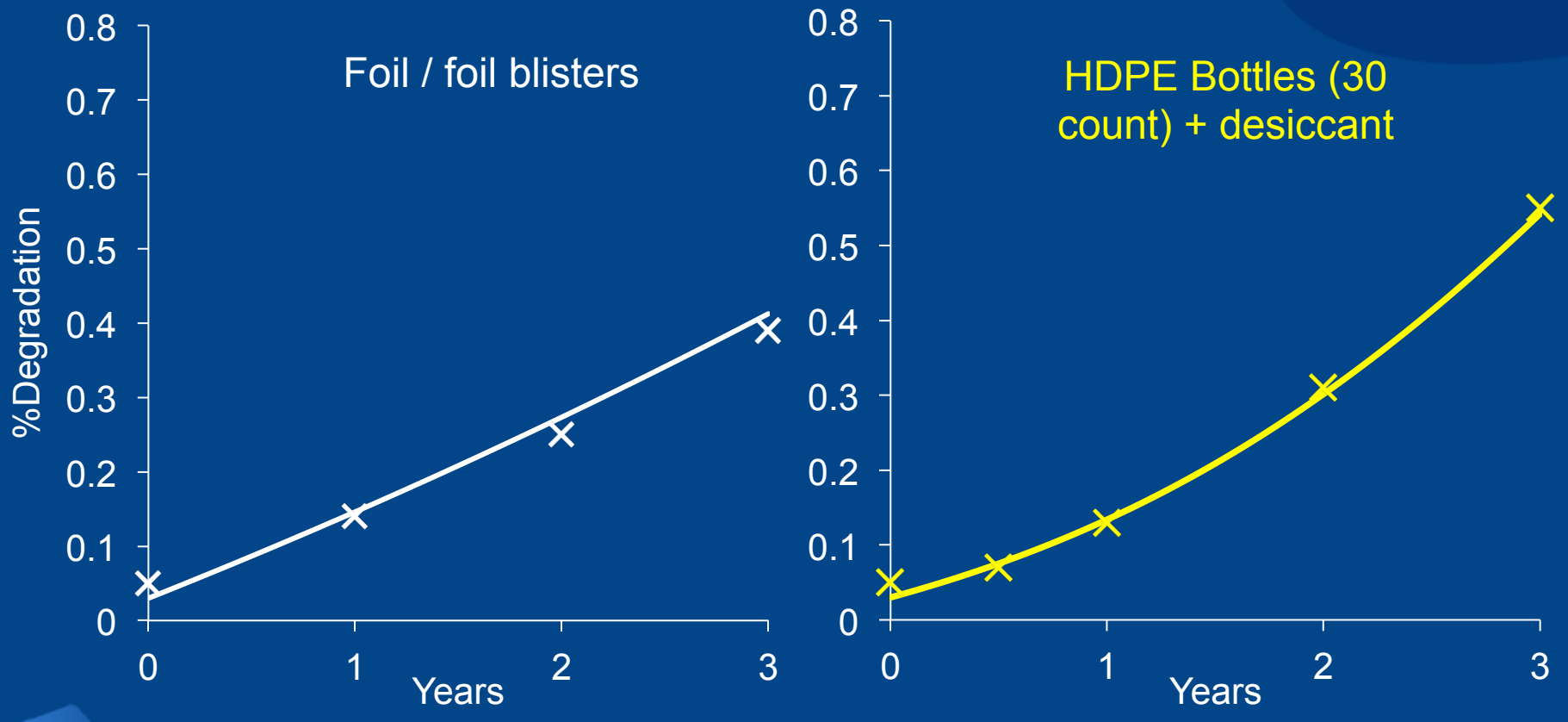
ASAP: How Well Does it Work?

Product	Degradant	Real Time	ASAP Prediction	Comments
Product A- MR Tablets 9 months, 25°C/60%RH	A1	4.1%	4.2% ± 0.84	Hydrolysis
	A2	1.5%	1.2% ± 0.24	Esterification
Product B- 5mg Tablets 12 months, 30°C/75%RH	B1	0.02%	0.07% ± 0.02	Oxidative degradation
Product B- 1mg Tablets 12 months, 30°C/75%RH	B1	0.05%	0.29% ± 0.1	Oxidative degradation
Product C- 100mg IR Tablets 3 months, 25°C/60%RH	C1	5.3 ppm	6.2 ppm ± 1	Low- level oxidative degradant
Product A- Oral Solutions (5 Formulations) 7 months, 5°C	A1	1. 0.56% 2. 0.35% 3. 0.47% 4. 0.32% 5. 0.53%	1. 0.60% ± 0.03 2. 0.36% ± 0.01 3. 0.61% ± 0.03 4. 0.30% ± 0.02 5. 0.69% ± 0.03	Hydrolysis
Product D- Oral Solution 2 years, 30°C	D1	0.31%	0.4% ± 0.08	Lactam formation

ASAP: How Well Does it Work?

Product	Degradant	Real Time	ASAP Prediction	Comments	
Product E- Patch 6 months, 40°C	E1 E2 E3	0.15% 1.72% 0.89%	0.12% ± 0.08 1.19% ± 0.24 0.88% ± 0.17	Prod D- formamide Acetyl- Prod D Hyrdoxy- Prod D	
Product F- Tablets 2 years, 25°C/60%RH	F1	0.70	0.98% ± 0.08	Hydrolysis	API Qualifications, Root Cause Investigative studies & Formulation Screenings
2 years , 30°C/75%RH		1.51	1.93%± 0.16		
6 months, 40°C/75 %RH		4.80	3.85% ± 0.24		
Product G - POS 6 months, 40°C/75%RH	G1	(106.7 mg/g) 3% potency loss	(103.4 mg/g) 6% potency loss	Hydrolysis	Tech Transfer & API Qualification
Product H- Tablets 4 years, 25°C/60%RH	H1 H2	0.22% 0.06%	0.22% ± 0.06 0.07 %± 0.02	Lactam formation Ester (Lactone) formation	Proposed Package Changes, Shelf Life Extension & Replacement of Annual Stability Commitments
Product I- 100mg Tablets 2 years, 25°C/60%RH	I1	0.01%	0.01% ± 0.01	Oxidation	
Product J- Capsules 2 years, 25°C/60%RH	J1	0.08	0.08%± 0.0	Lactam formation	
Product K- Capsules 3 years, 25°C/60%RH	K1	0.03	0.03%± 0.10	Oxidation	

ASAP: How Well Does it Work?



Product L (45 mg tablets) stored at 30°C/75%RH

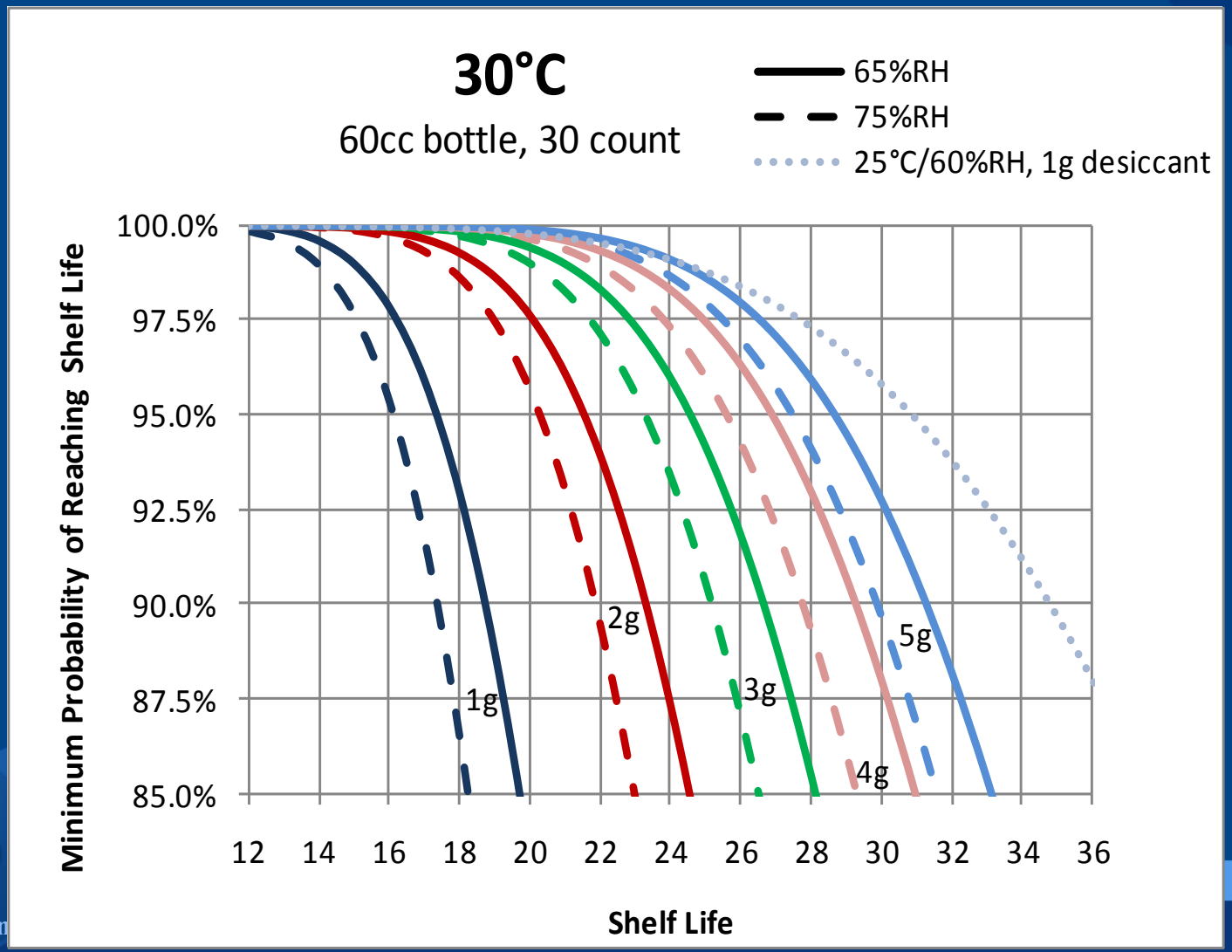
Example Applications of ASAP (1)

- Accurate prediction of shelf-life of API and drug products. ASAP can be used to set interim use-periods (e.g. for IMPDs and INDs).
  - Unpackaged Study (no delay in starting the study), 14 day protocol
- During Development: Helps to quantify stability risks and accelerates development:
  - Quantifies the effects of temperature and humidity on stability performance (e.g. “10% increase in RH or 10ºC increase in temperature increases rate by x-fold”)
  - Allows the stability impact of any changes throughout development to be rapidly assessed.
    - Formulations/processes
    - Synthetic routes
    - Assessing batch-batch equivalence of API and drug products
  - Reduces or eliminates the need to wait for long-term stability readouts at key timepoints during development
- Packaging Selection. This is a major benefit of the ASAP approach: the stability performance in any pack-type can be predicted and compared ‘at the touch of a button’ (all that is needed is the MVTR of the pack-type). The need to conduct expensive, lengthy packaging selection studies is reduced or eliminated.
- Prediction of Stability in any Climatic Zone. The effect of changing storage conditions from (e.g.) 25ºC / 60% RH to (e.g.) 30ºC / 75% RH can be assessed and the risks quantified.

Example Applications of ASAP (2)

- At Registration
  - Use ASAP as supportive data or as an alternative to traditional stability to minimize stability commitments
  - Use diagnostic tools to demonstrate applicability of the ASAP model applied for each drug product
- QBD for Stability:
  - ASAP / Packaging Tool is in-line with the QBD principle of understanding and modelling the effects of parameters that may affect stability performance (e.g. temperature and humidity).
  - ASAP can also be used as a tool for rapidly quantifying the stability effects of changes to the product or process (e.g. ref. Kougoulos et. Al., AAPS PharmSci Tech, 2011) QBD for Stability.
- Post-Approval
  - Use ASAP as part of post-approval change protocol
  - Annual stability commitments: costs / overheads can be reduced

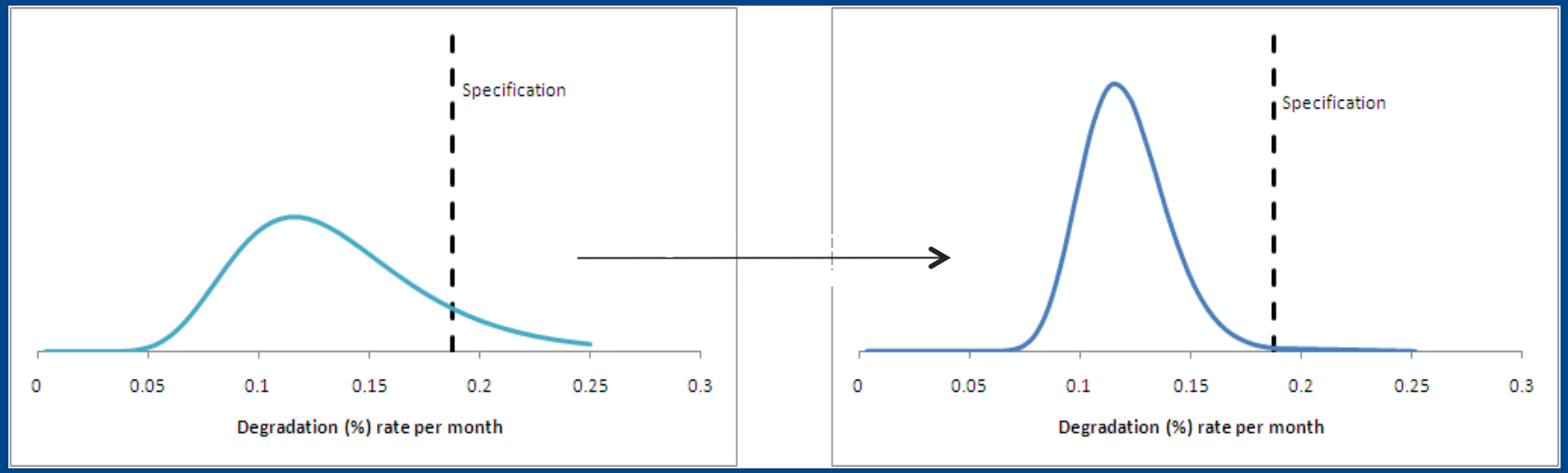
Case Study 1: Global Registration, Climatic Zone 4 and Package Selection



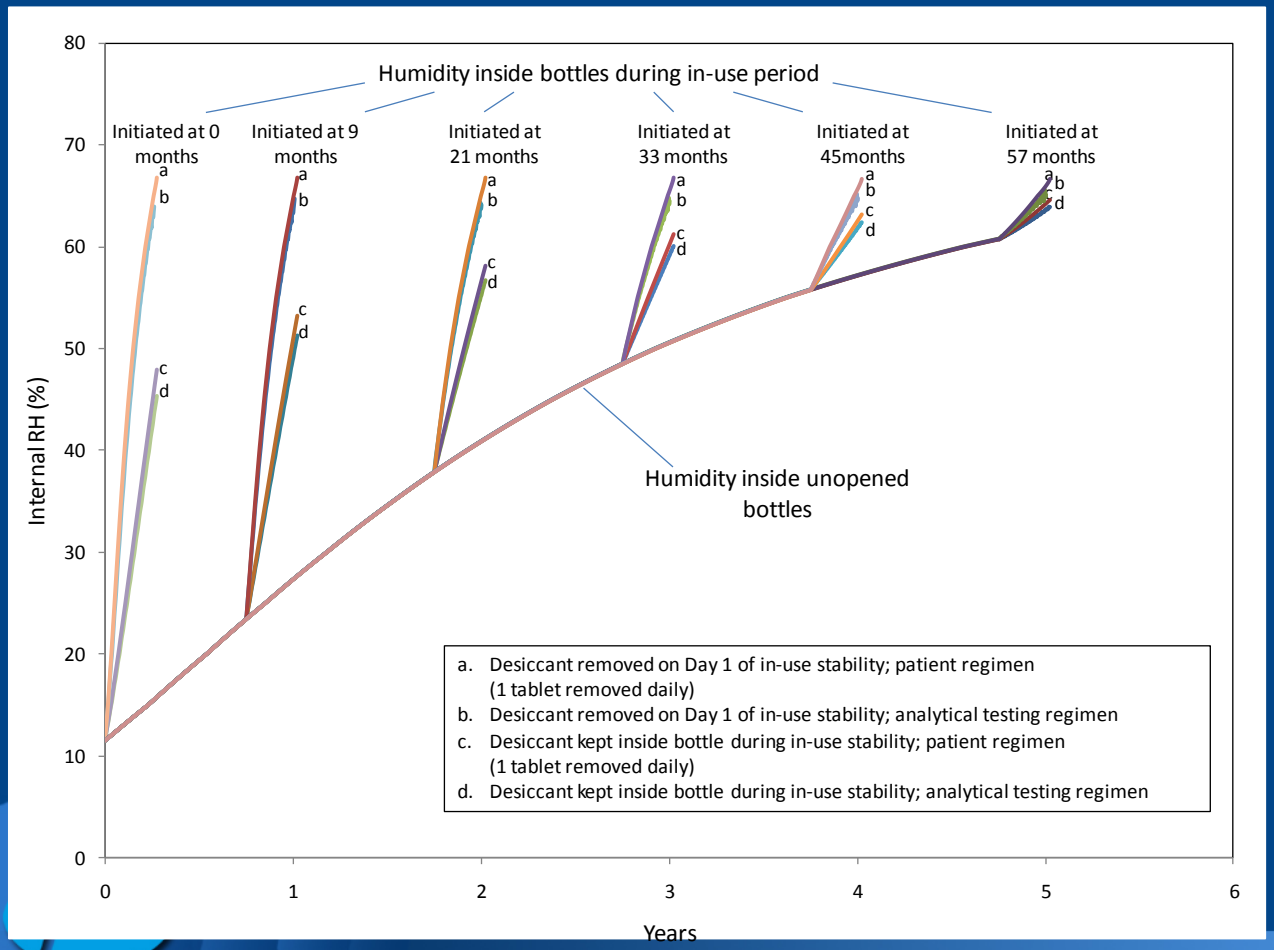
Case Study 2:

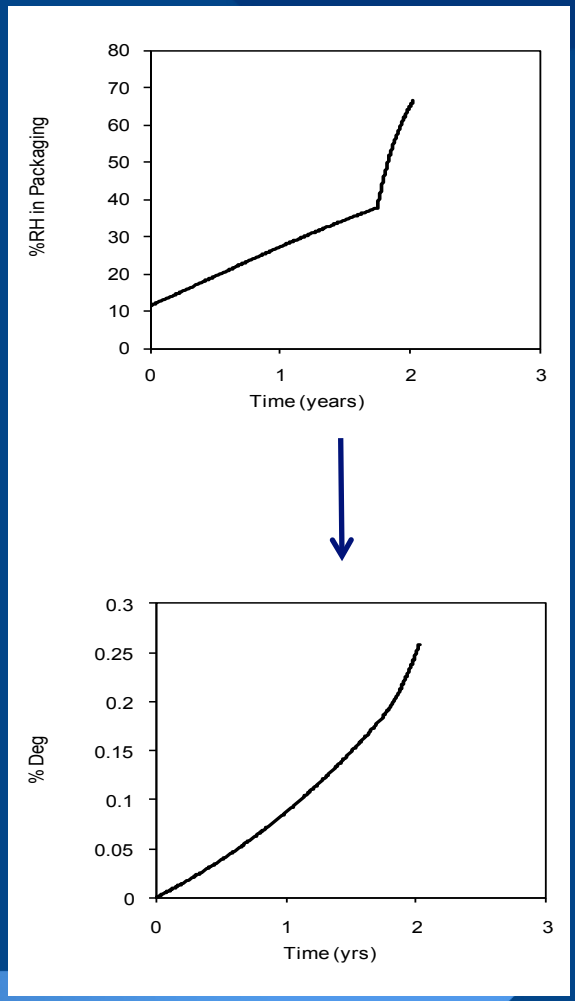
Using ASAP to understand and quantify the effect of different extents of drying of a wet-granulated product

- Tighter control of water activity at point of packaging reduces batch-batch variability



Case Study 3: Simulation of In-Use Stability





Case Study 4: Temperature Excursions

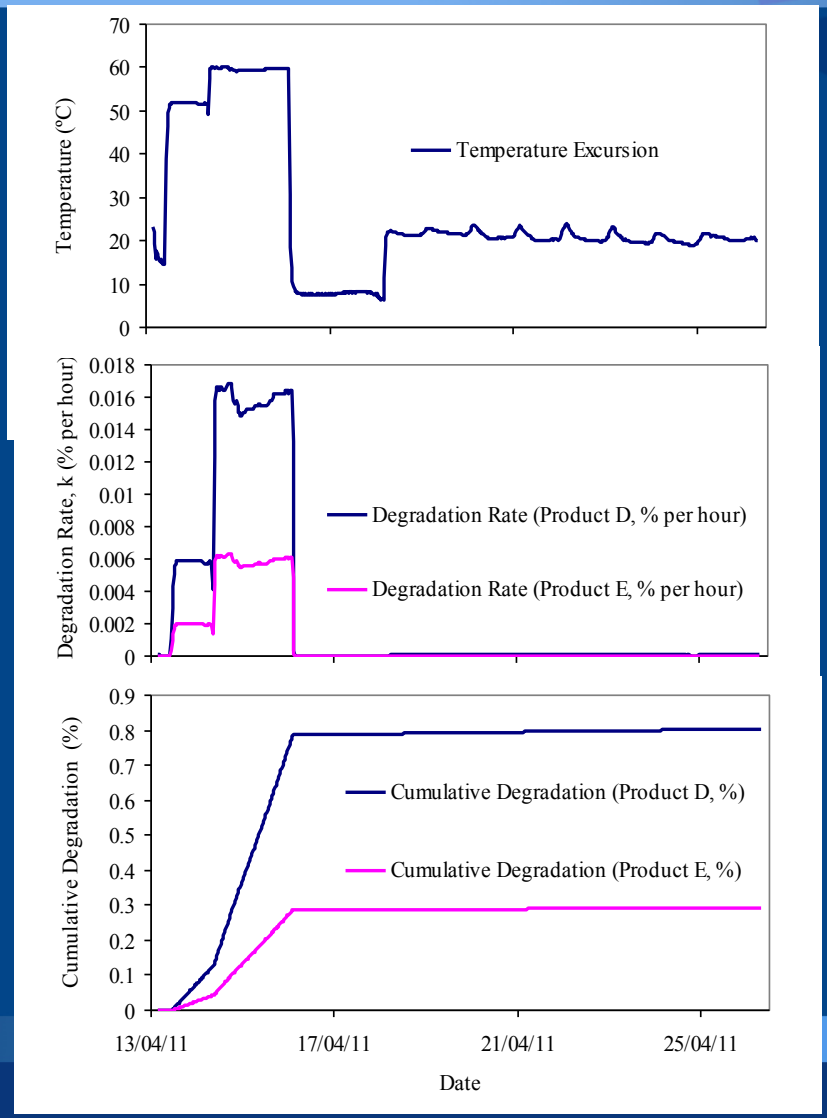
Temperature Logger data

↓ **A, E_a**

Degradation Rate

↓ Cumulative

% Degradation
(as measured by e.g. HPLC)



Thank you For Listening

Questions / Discussion

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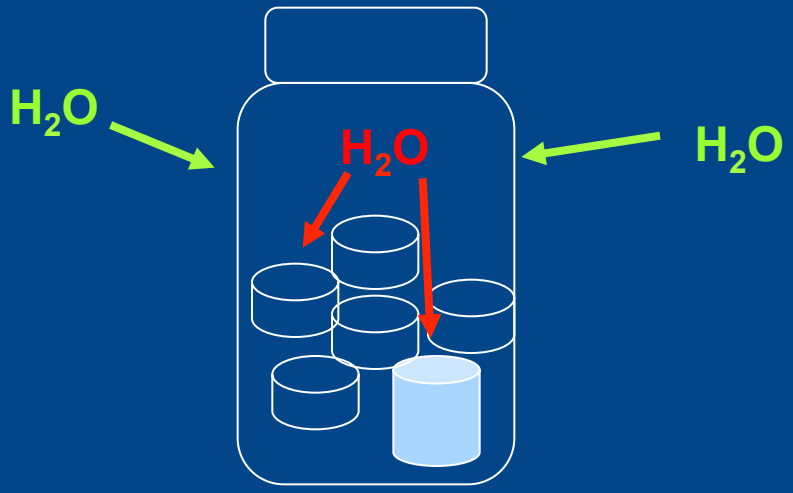
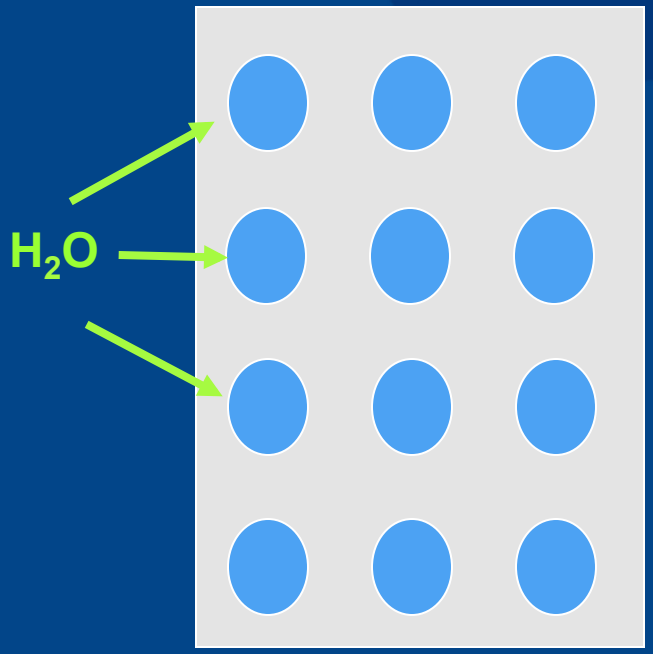
http://www.linkedin.com/pub/garry-scrivens/17/8a0/4a1

Packaged-Product Stability





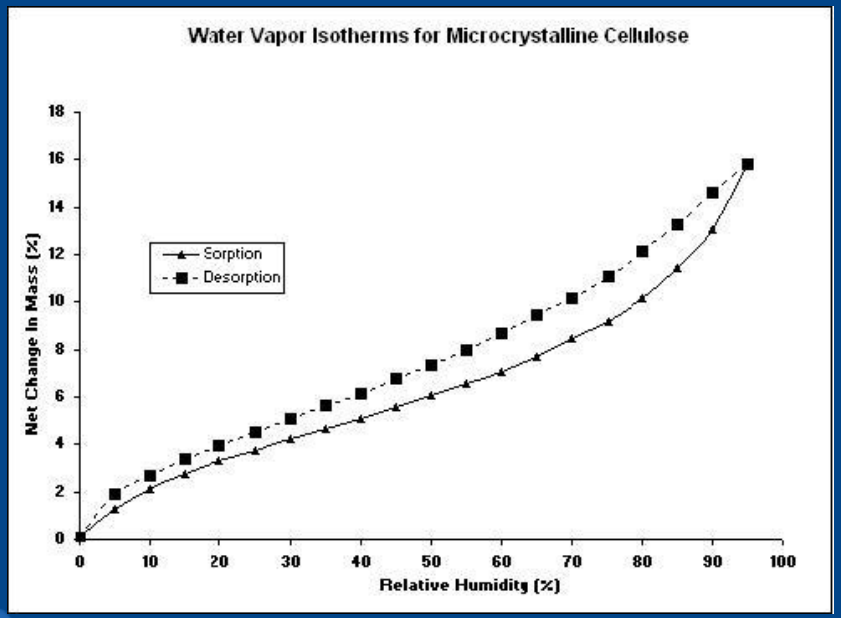
Moisture transfer depends on MVTR, ΔRH and temperature

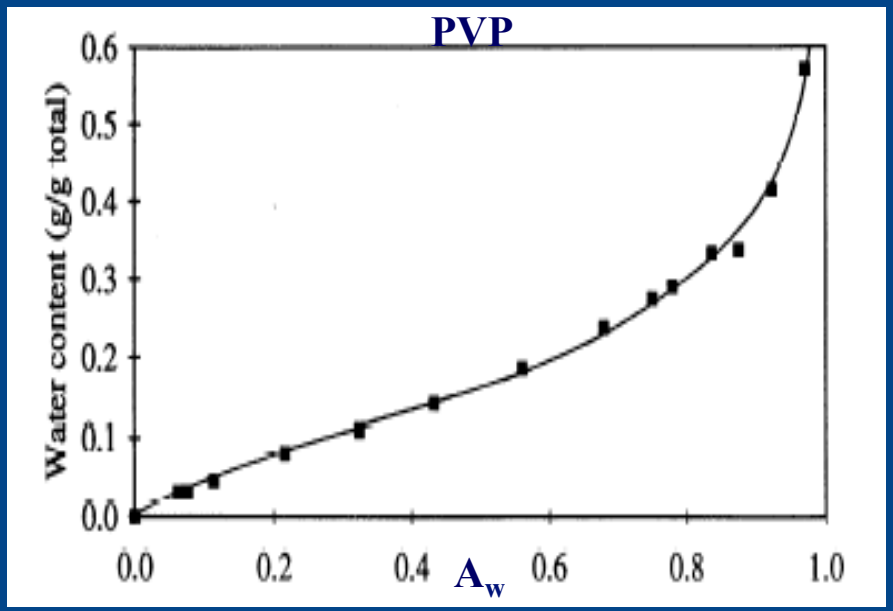
MVTR = P. ΔRH

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

Moisture Vapour Sorption Isotherms

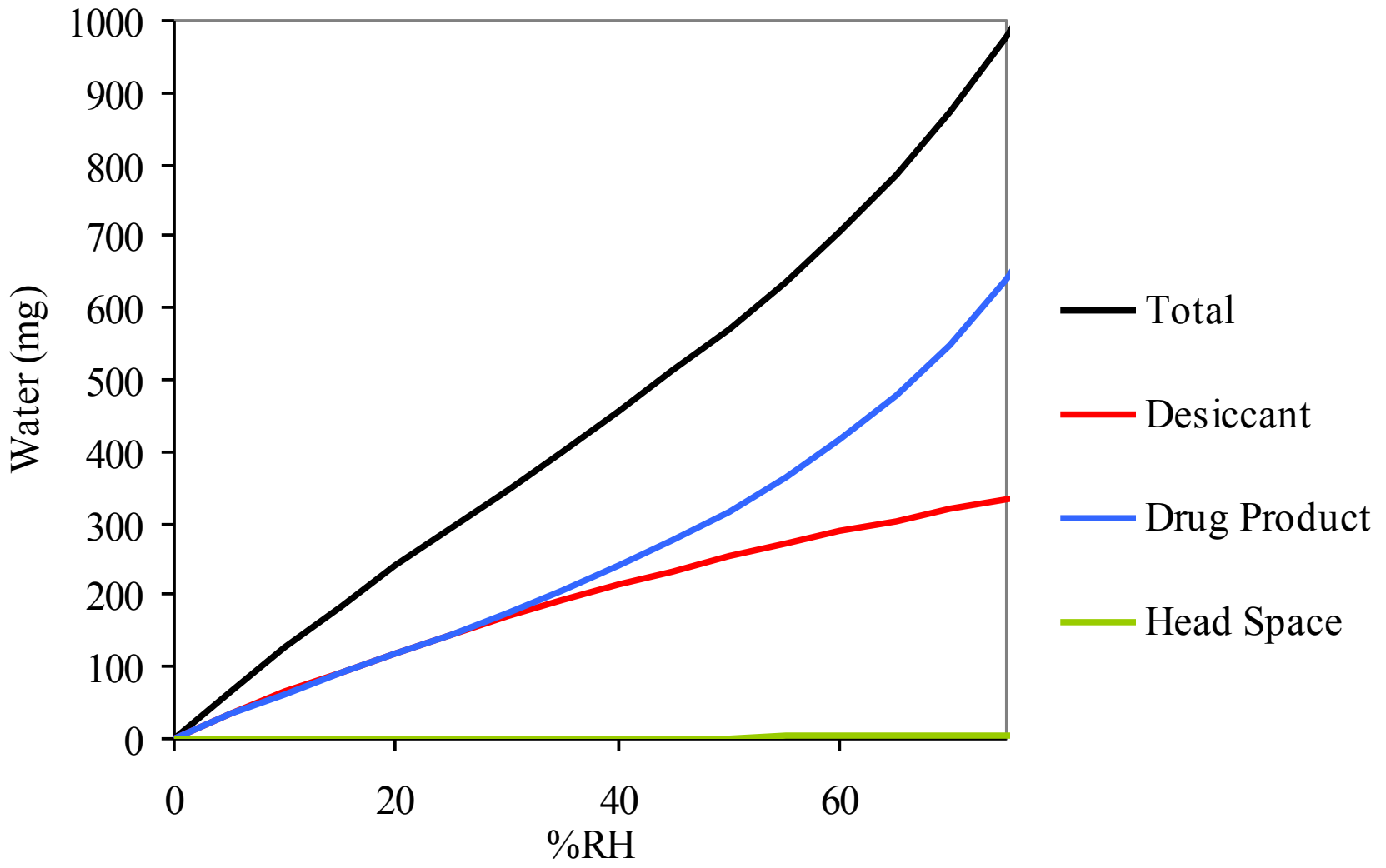
- The water content varies with water activity, A_w (≡ %relative humidity) according to the '*water vapour sorption isotherm*' for the material, e.g.:





- GAB parameters are used to describe water vapour sorption isotherm curves

Moisture Vapour Sorption Isotherms

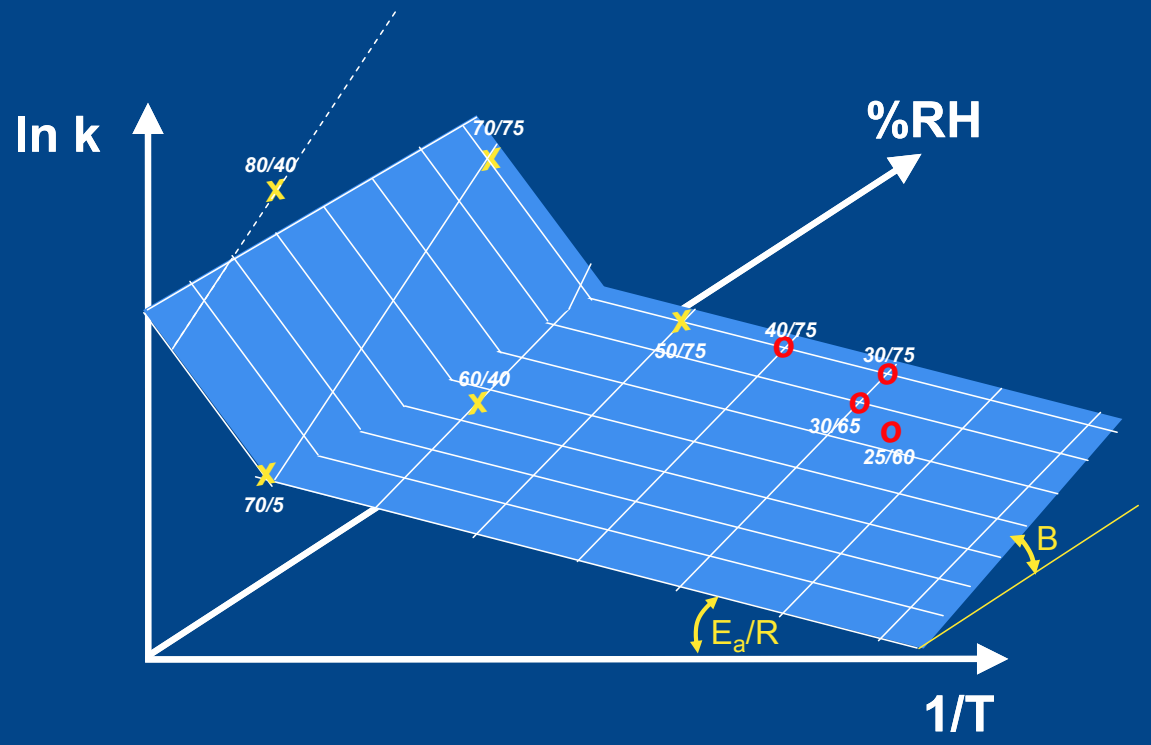


Potential Pitfalls

1. Non-isoconversion
2. Form / Phase changes caused by temperature and/or humidity (e.g. melts, glass transitions, anhydrate / hydrate formation, deliquescence etc.)
3. Secondary Degradation (consecutive reactions)
4. Competitive Processes
5. Significant contribution to overall degradation from multiple API environments that have significantly different E_a and B parameters
6. Significant contribution to overall degradation from multiple degradation pathways that have significantly different E_a and B parameters
7. Combinations of the above

Potential Causes of Poor Fit / Prediction

Form / Phase changes caused by temperature and/or humidity (e.g. melts, glass transitions, anhydrate / hydrate formation, deliquescence etc.)



Potential Causes of Poor Fit / Prediction

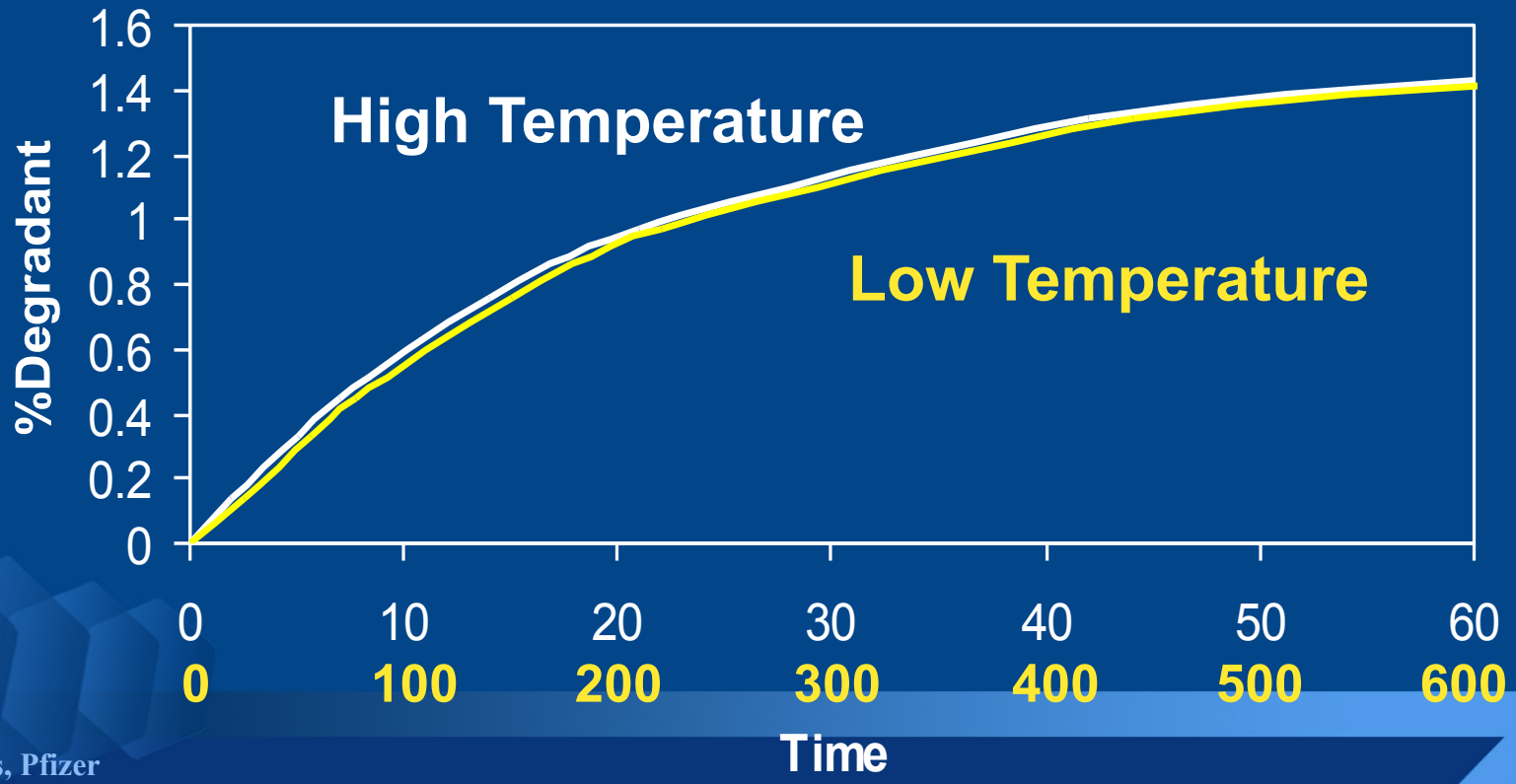
ASAP %RH condition(s) exceed *Critical Relative Humidity, CRH* (e.g. of one of the excipients), which leads to *deliquescence*.

Excipient	CRH @ 20ºC	CRH @ 40ºC
PEG 3350	94	85
Dextrose	100	88
Fructose	72	64
Sorbitol	80	69
Sucrose	86	83
Xylitol	91	73
Tartaric Acid	85	78
Potassium Chloride	84	82
Sodium Chloride	75	75
Sodium Citrate	61	78

Potential Sources of Inaccuracy: Degradation Kinetics at Different Conditions

For a given system, the *shape* of the curve (i.e. degradation kinetics) is usually very similar across different stability conditions, just the timescale is different …

…sometimes this is not the case



Potential Sources of Inaccuracy: Complex systems

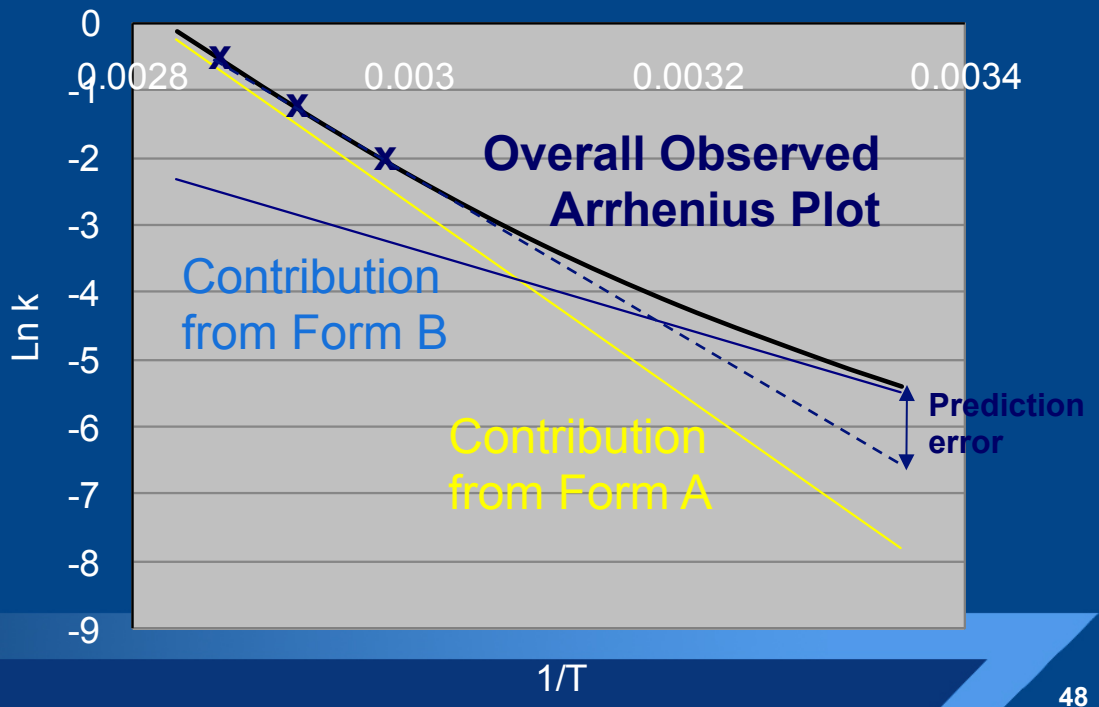
Significant contribution to overall degradation from multiple API environments that have significantly different E_a and B parameters

$API_{Form\ A}$ —(k_A $f(E_{a,A}$ and $B_A)$)→ Deg Prod

$API_{Form\ B}$ —(k_B $f(E_{a,B}$ and $B_B)$)→ Deg Prod

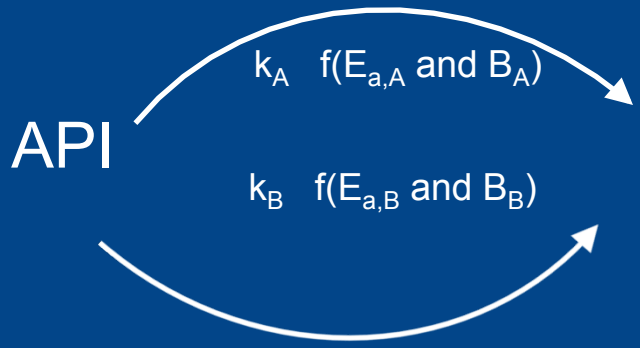
This problem can manifest as a curved Arrhenius plot.

This is rare because degradation usually derives predominantly from one form of API



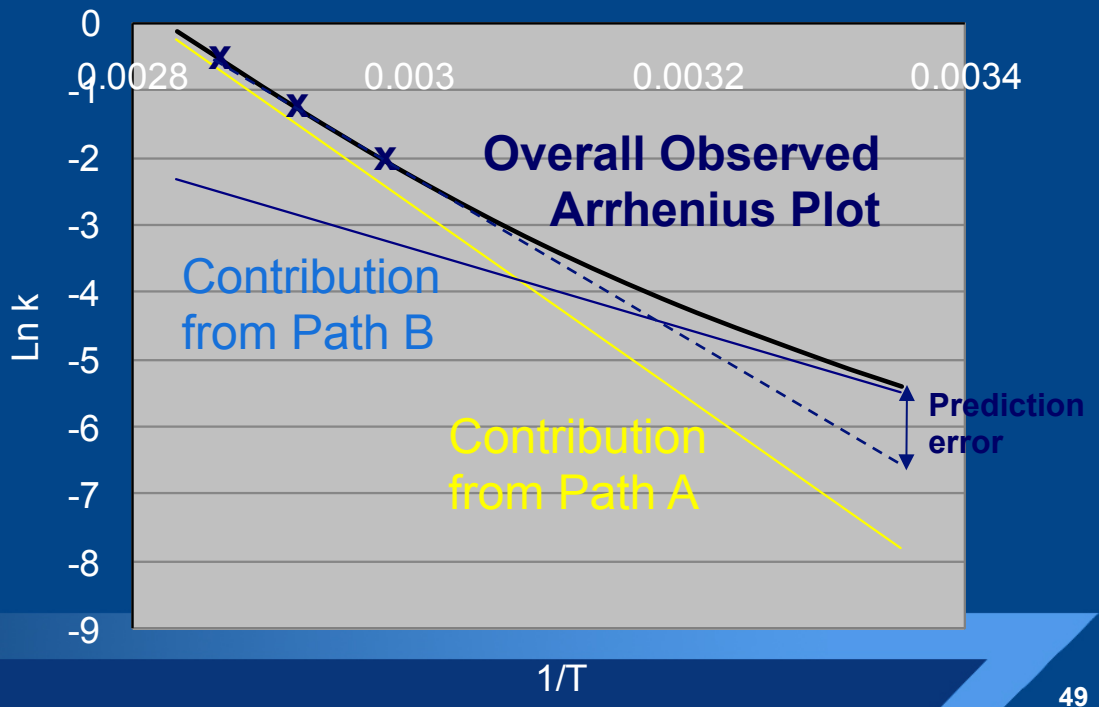
Potential sources of Inaccuracy: Complex Systems

Significant contribution to overall degradation from multiple degradation pathways that have significantly different E_a and B parameters



This problem can manifest as a curved Arrhenius plot.

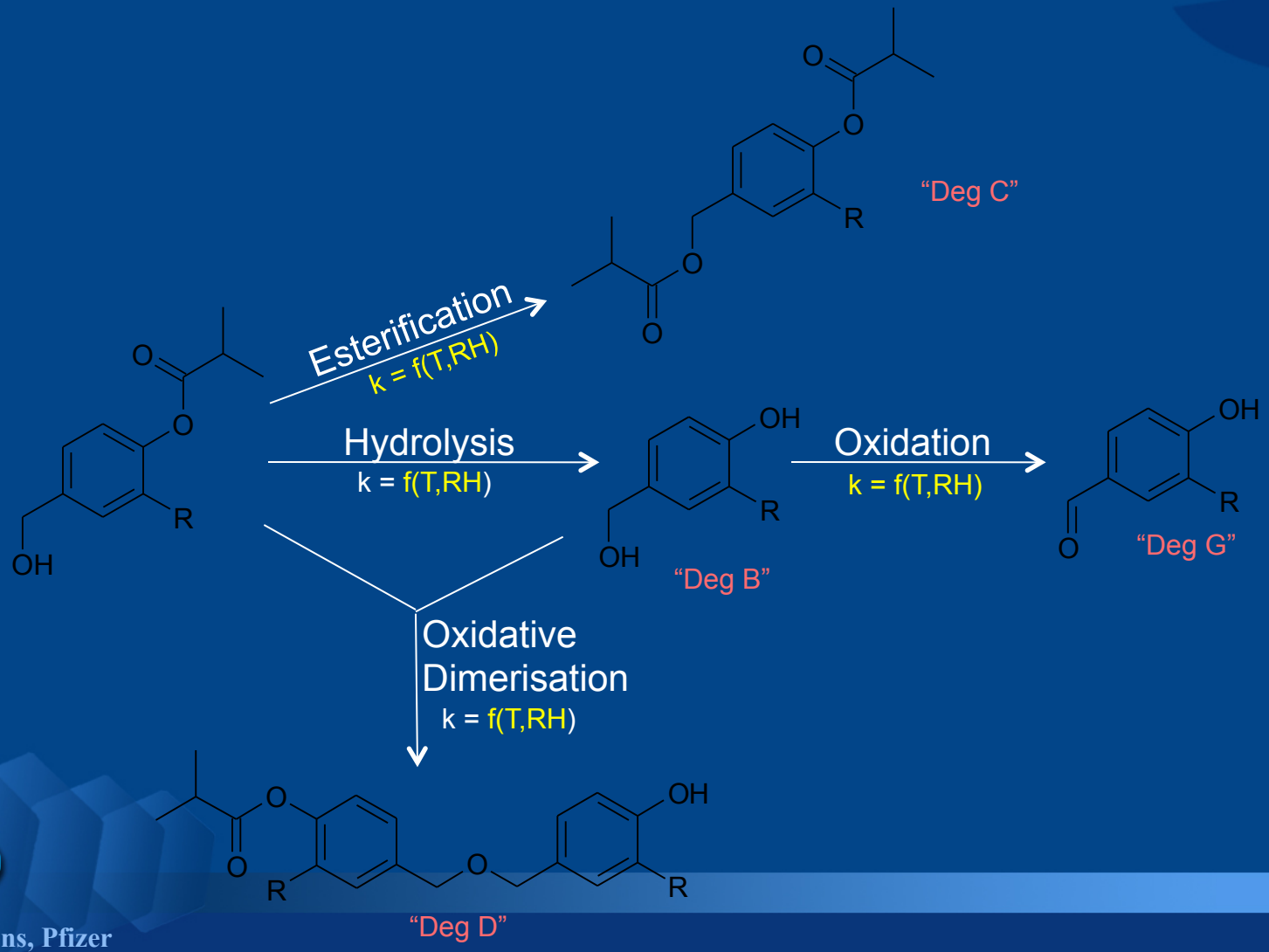
This is rare because degradation usually derives predominantly from a single pathway



Complex Systems:

Competitive and Consecutive Processes

Kinetic Simulations



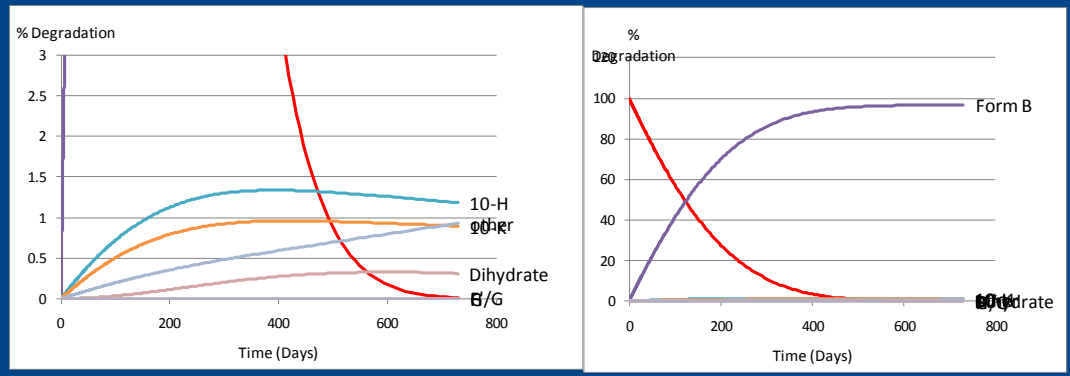
Complex Systems:

Competitive and Consecutive Processes

Kinetic Simulations

Form A (unstable form)	→	Form B (stable form)	(nucleation-type kinetics)
Form A	→	10-H (degradation product)	(1° kinetics)
Form A	→	10-K (degradation product)	(1° kinetics)
10-K	→	Other Degs	(1° kinetics)
Form B	←→	Dihydrate	(nucleation-type kinetics)
Etc.			

30°C/65%RH,
30-count 60cc HDPE bottle
No Desiccant:



25°C/60%RH,
30-count 60cc HDPE bottle
With Desiccant: