

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

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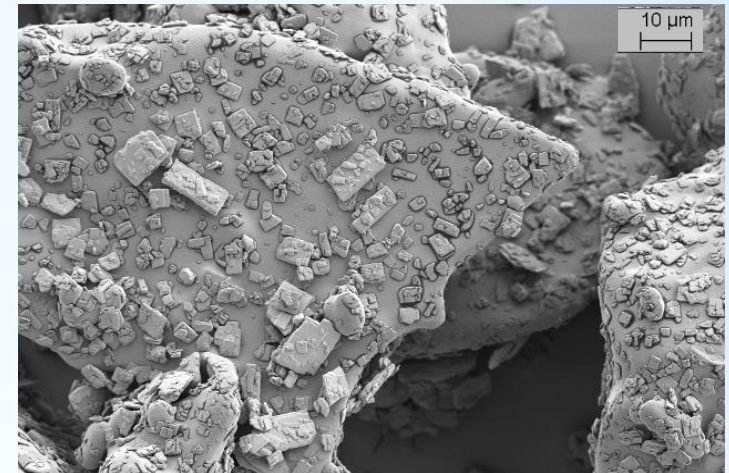


Outline

- **ASAPprime[®] Basic Principles**
 - Isoconversion
 - Moisture Sensitivity
 - Statistics
- **Packaging**
- **Future Additions to ASAPprime[®]**

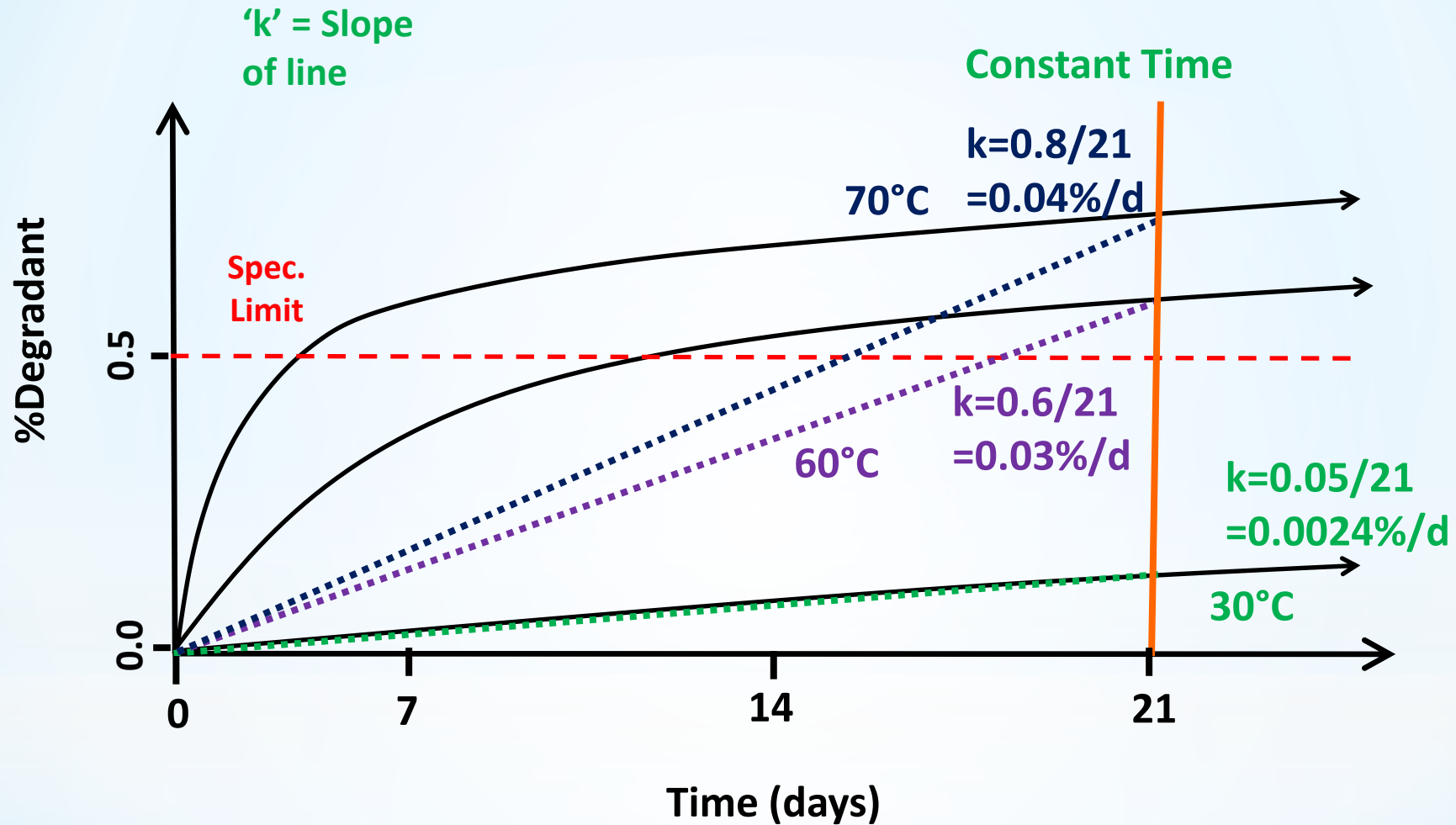
Complex Kinetics

- >50% products show complex kinetics
- **Example:** heterogeneous systems
 - Molecules in different microenvironments
 - crystal lattice
 - surface
 - amorphous
 - solid-solution
 - Multiple k's (multiple rate constants)

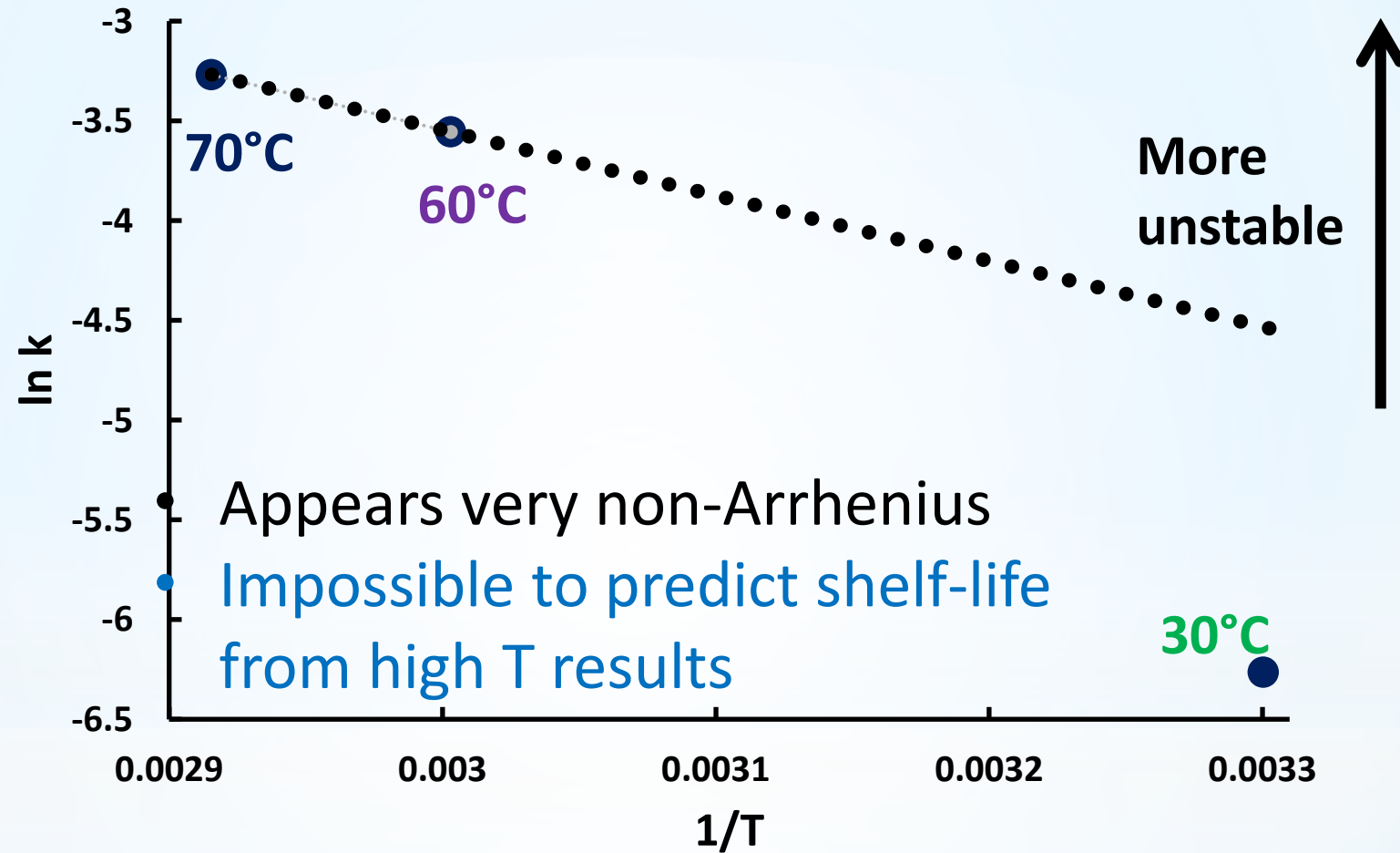


$$[P_t] = \sum_i k_i t \quad (\text{different } k \text{ for each API state})$$

Traditional Accelerated Stability

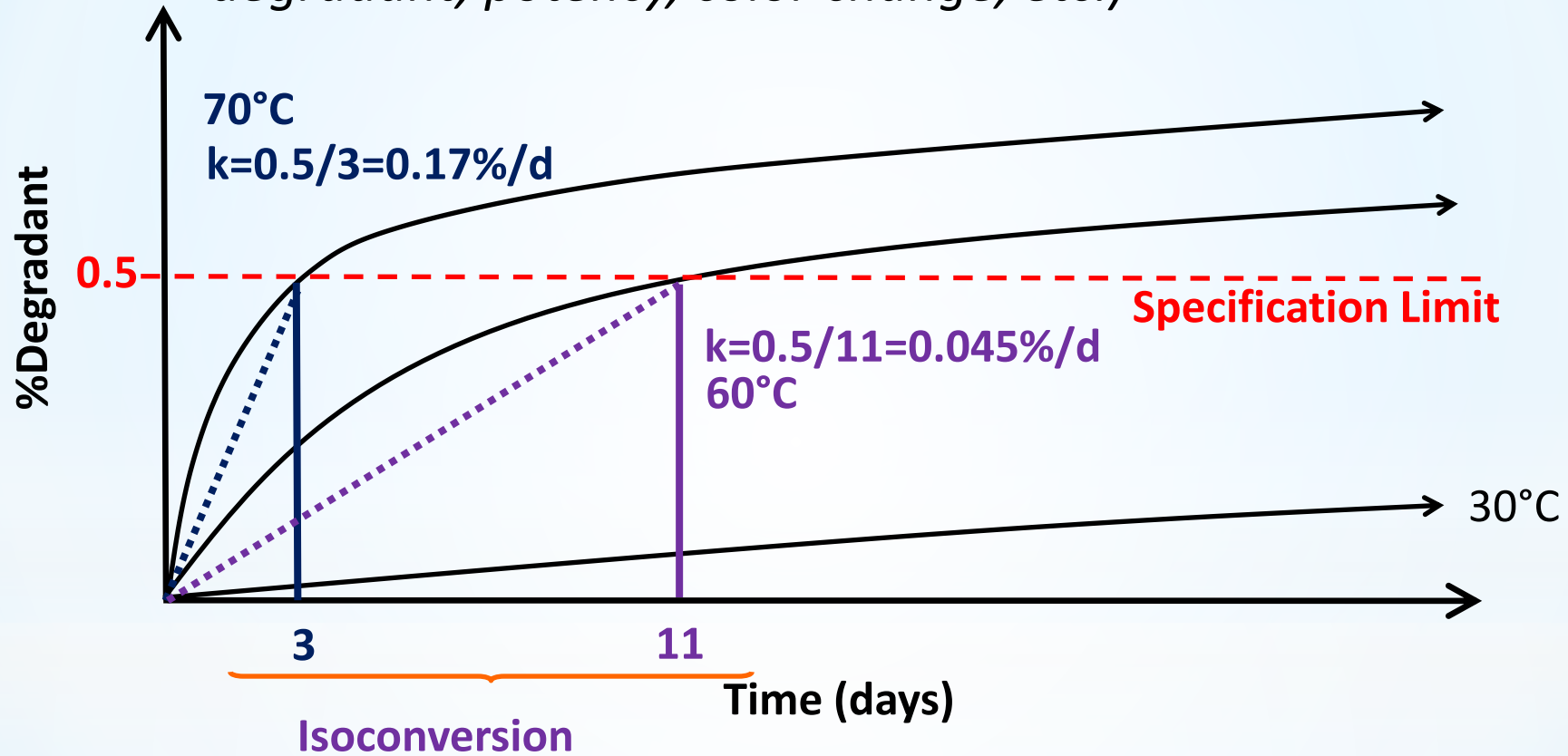


Traditional Accelerated Stability

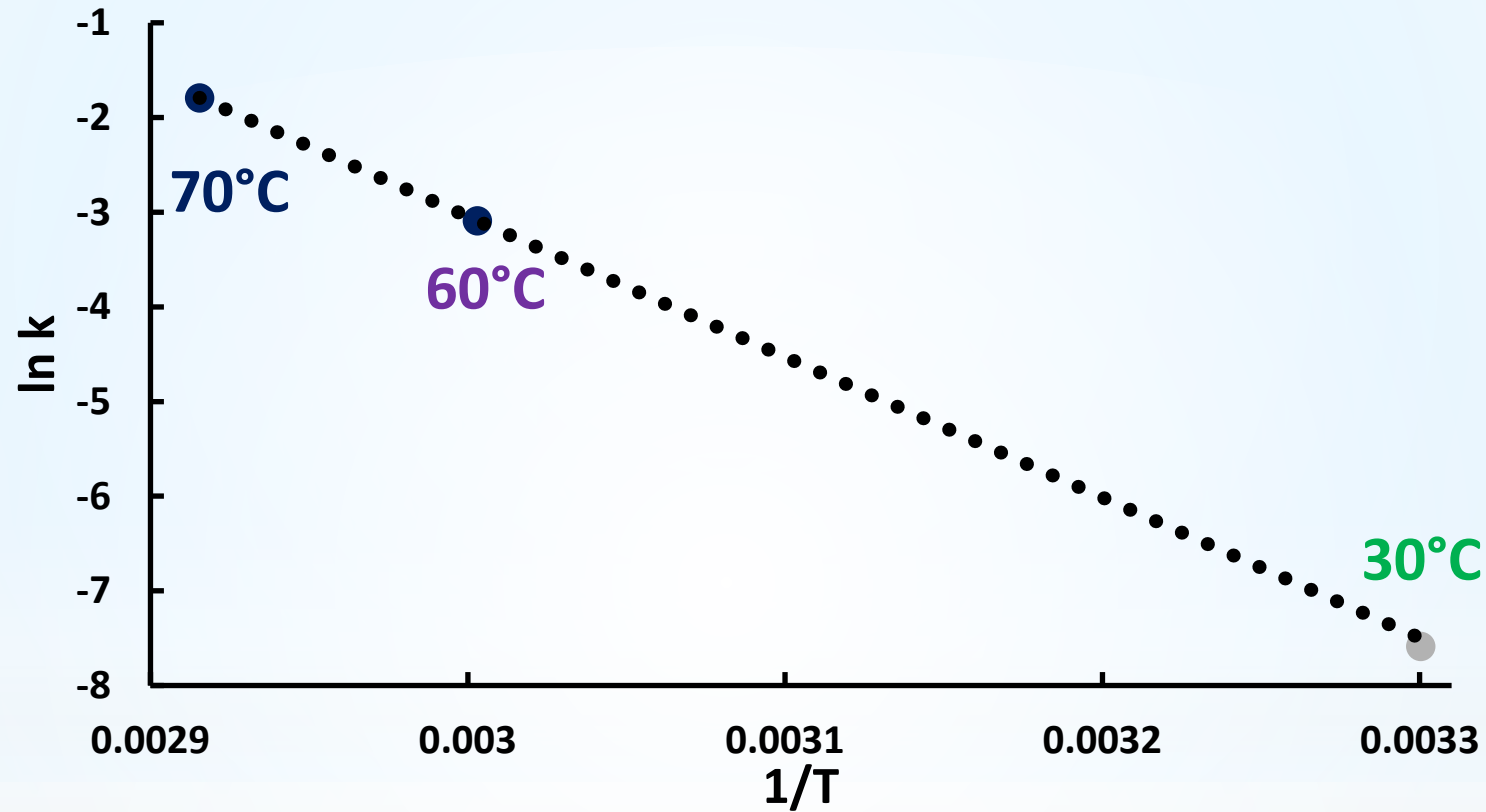


Isoconversion Accelerated Stability

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



Isoconversion Accelerated Stability



Accurate predictions do not depend on the kinetic form

Humidity Corrected Arrhenius Equation

collision frequency

humidity sensitivity factor

1.986 cal/deg

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

Spec. limit/(isoconversion time)

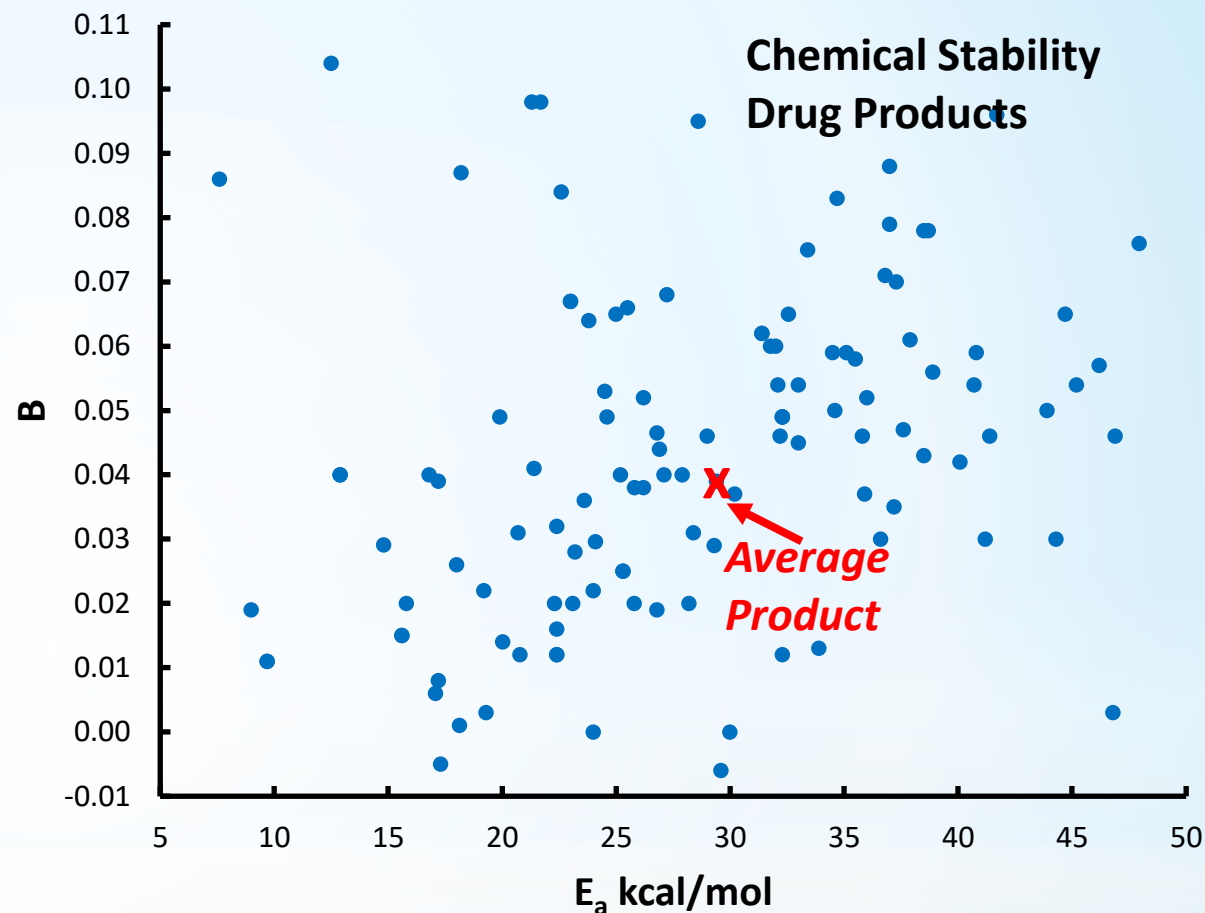
equilibrium relative humidity

activation energy

Impact of E_a and B on Shelf-Life

B	60%RH	65%RH	75%RH
0.00 low B	3.0 yrs	3.0 yrs	3.0 yrs
0.04 average B	3.0 yrs	2.5 yrs	1.6 yrs
0.09 high B	3.0 yrs	1.9 yrs	9.3 mos

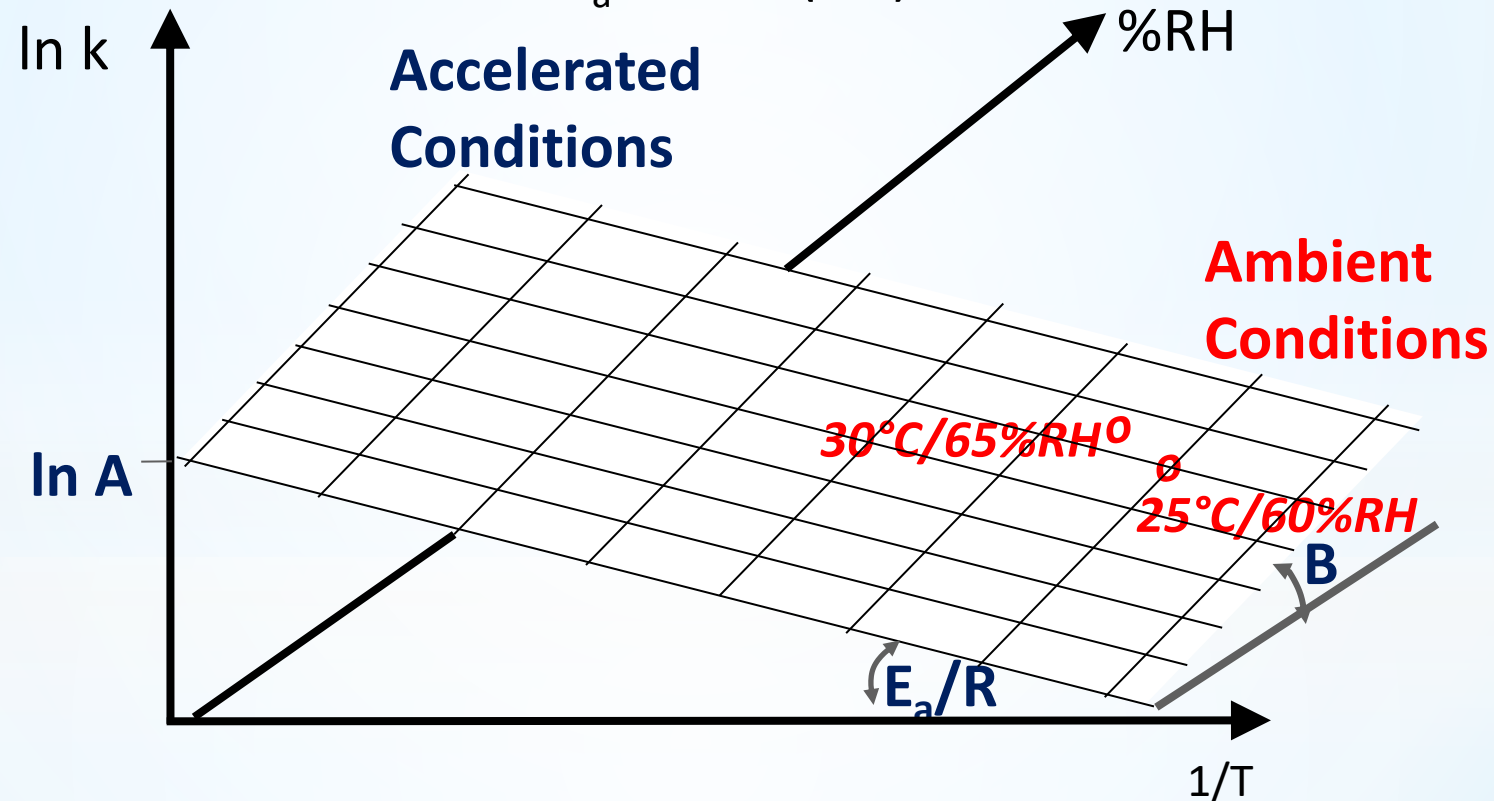
E_a	25°C	30°C	40°C
17 kcal/mol (71 kJ/mol) Low E_a	3 yrs	1.9 yrs	9 mos
29 kcal/mol (121 kJ/mol) Average E_a	3 yrs	1.3 yrs	3 mos
40 kcal/mol (167 kJ/mol) High E_a	3 yrs	1.0 yr	1 mo



Average product: 6 months 40°C/75%RH (open) = 9.5 years at 25°C/60%RH (open)

Accelerated Stability Assessment Program (ASAP) Design of Experiment: Determining the Plane

$$\ln k = \ln A - E_a/RT + B(\text{RH})$$



Experimental Setup

Mini-chambers:

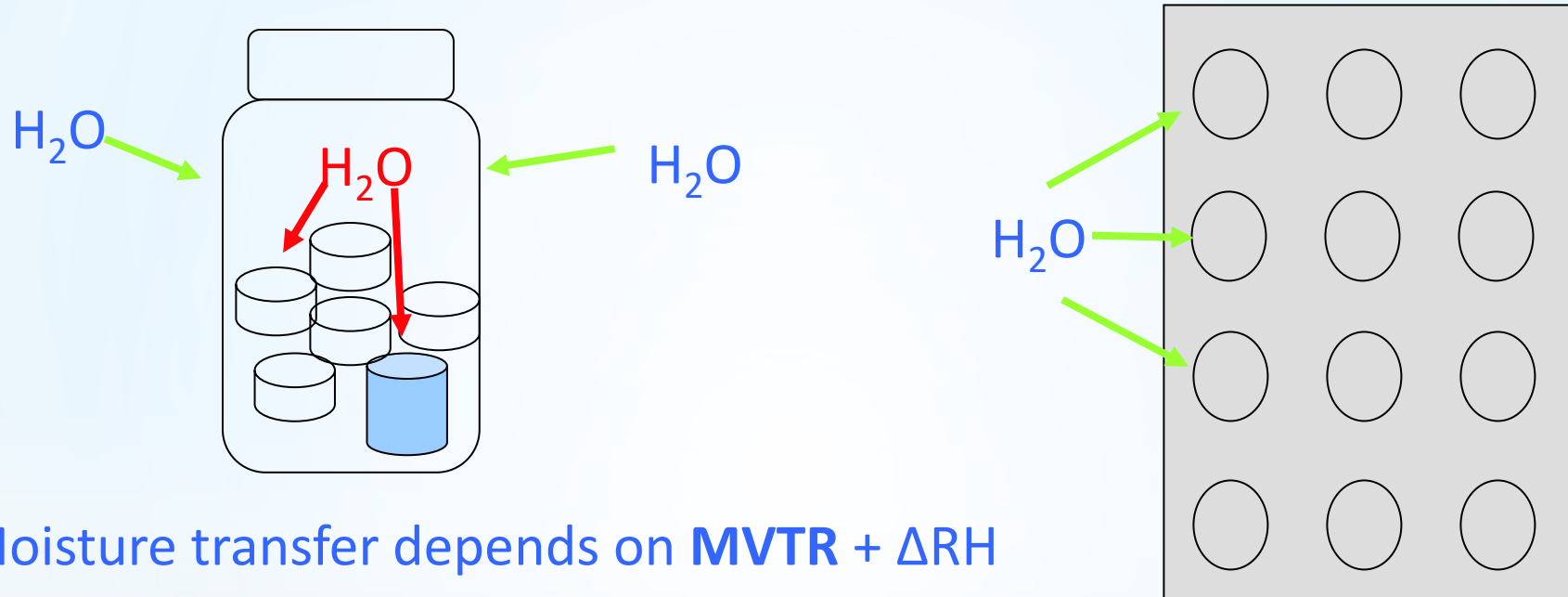
- Canning jars
 - Hold seals up to 95°C
 - Allow multiple RH conditions per oven
 - Prevent cross-contamination of samples
 - Allow for pre-equilibration of RH outside oven



Sample

**Saturated salt slurry:
in vial with moisture-
permeable cover**

Packaged-Product Stability



Moisture transfer depends on **MVTR + ΔRH**

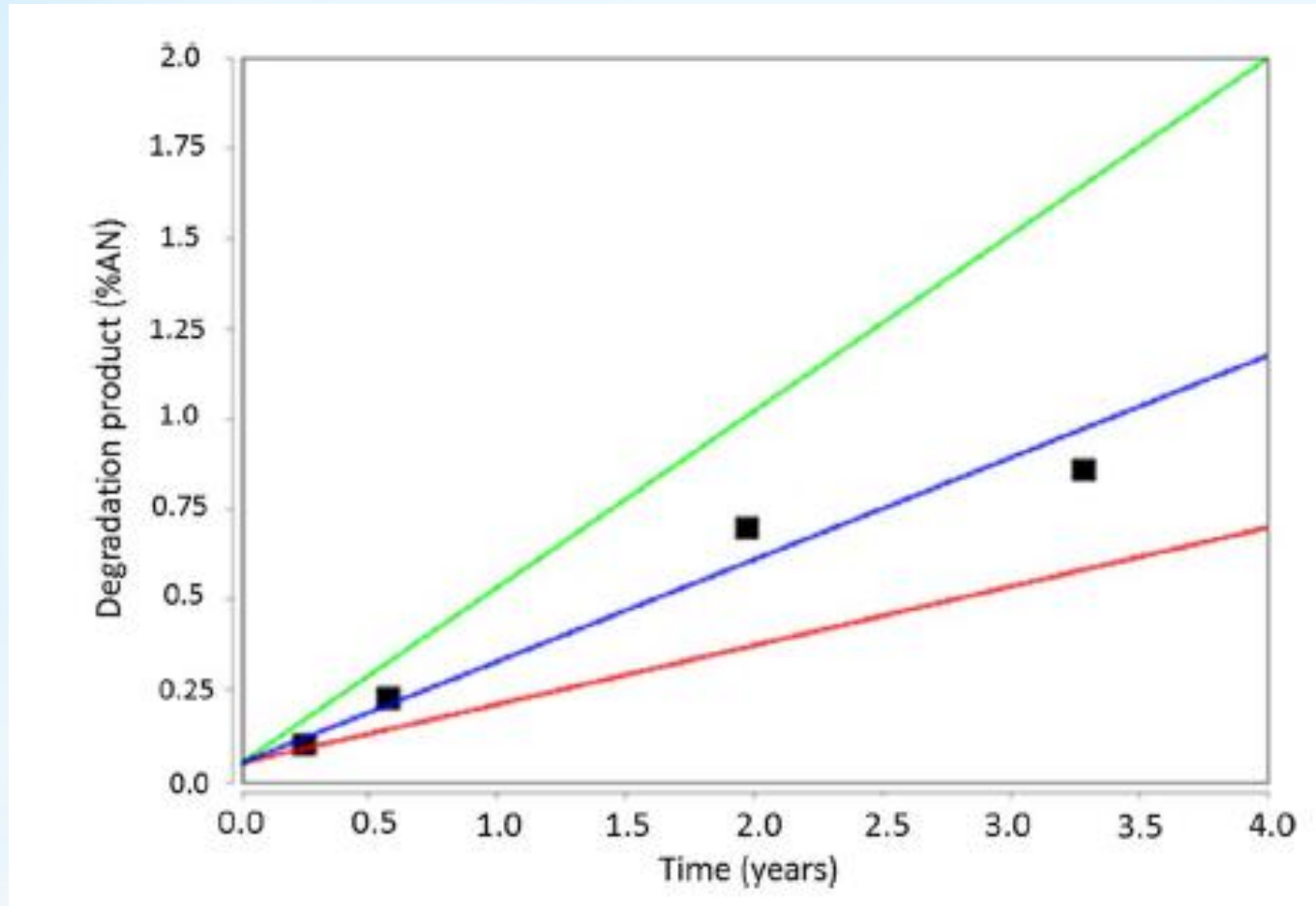
Moisture inside packaging equilibrates between headspace (RH), tablets, desiccant (**vapor sorption isotherms**)

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**

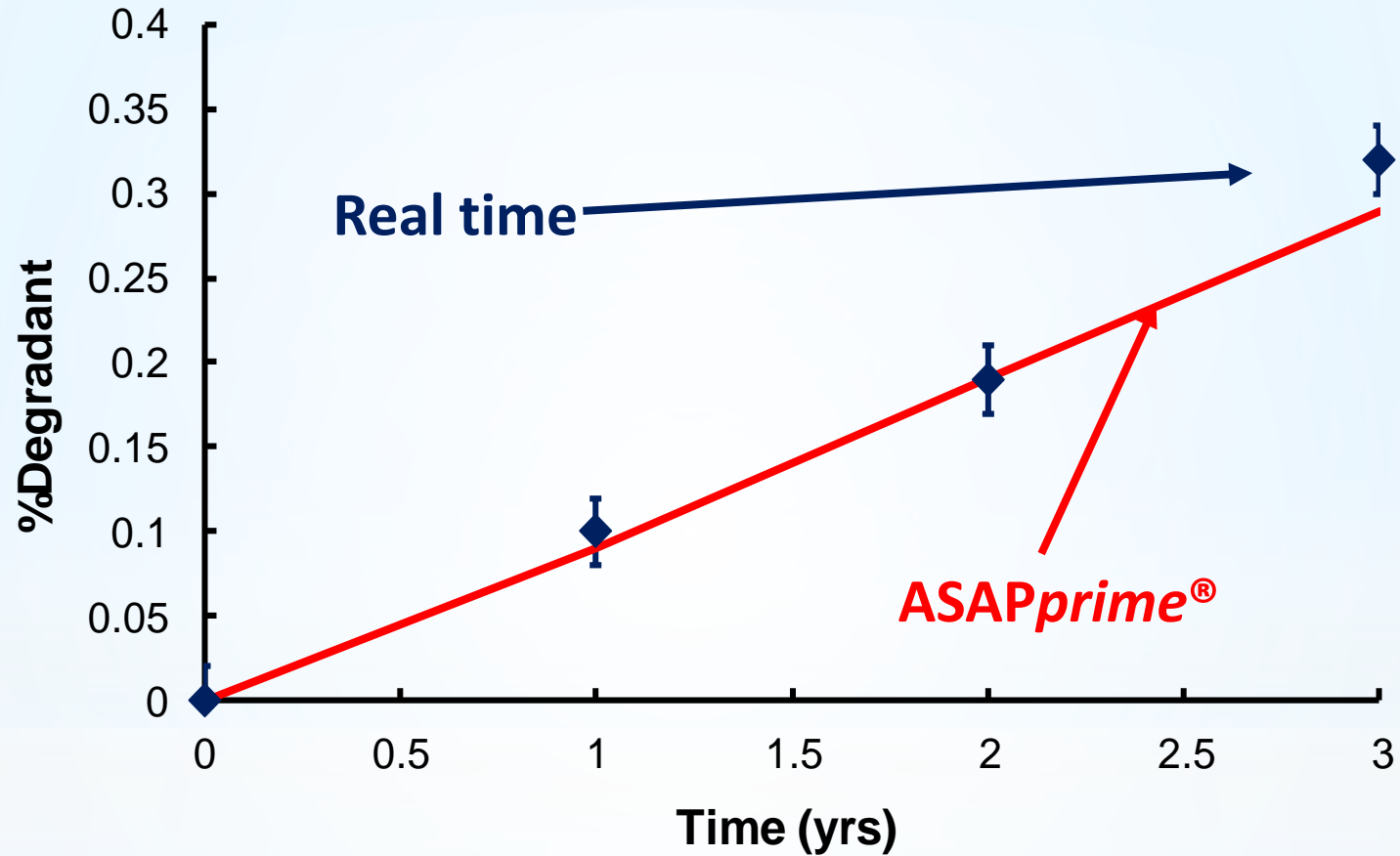
Example 1



Laroscorbine[®] liquid at 25°C

Legrand, et al., AAPS PharmSciTech 2021, 22:234

Example 2

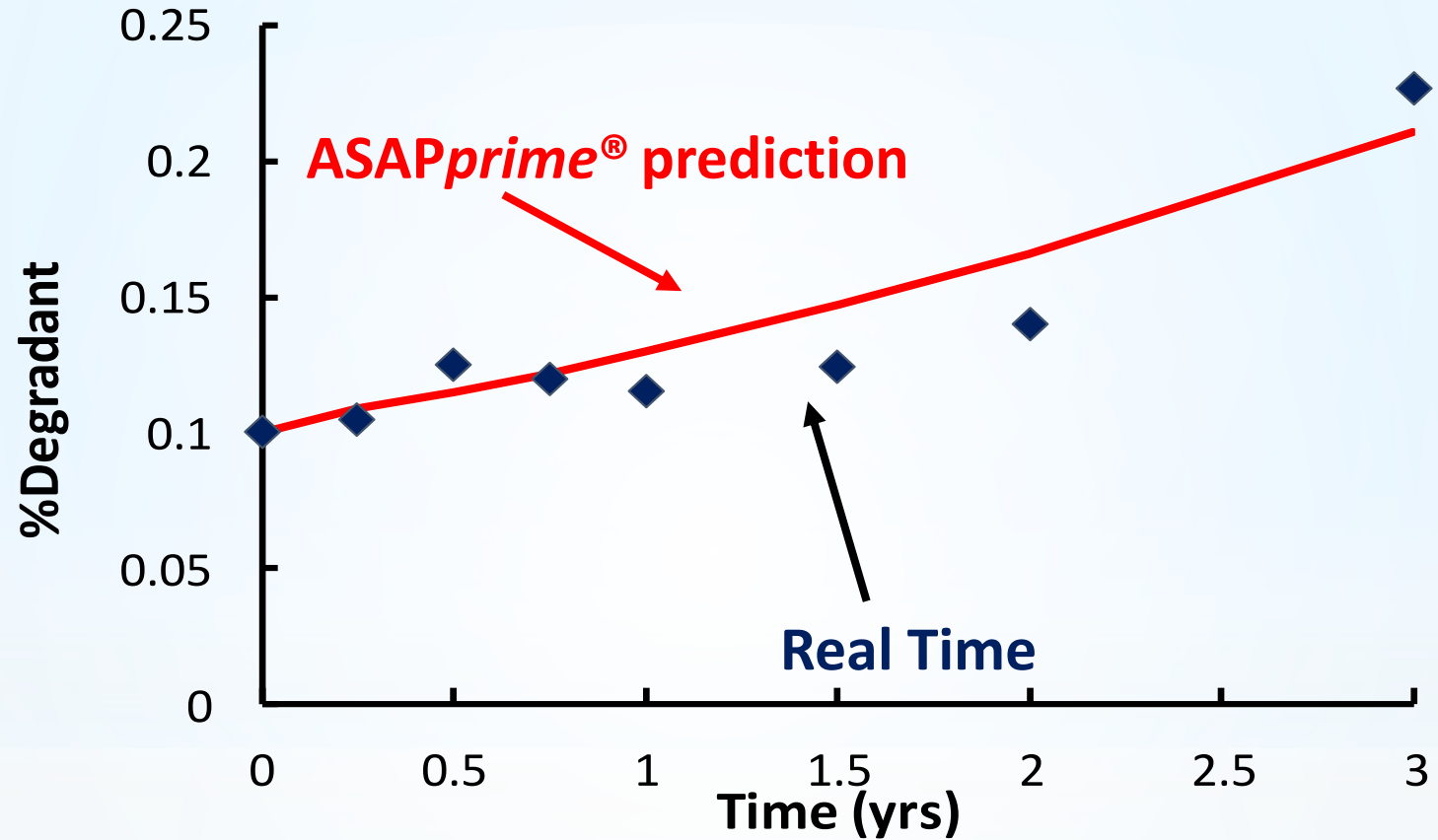


Drug Product Tablets; 30°C/65%RH

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Example 3

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



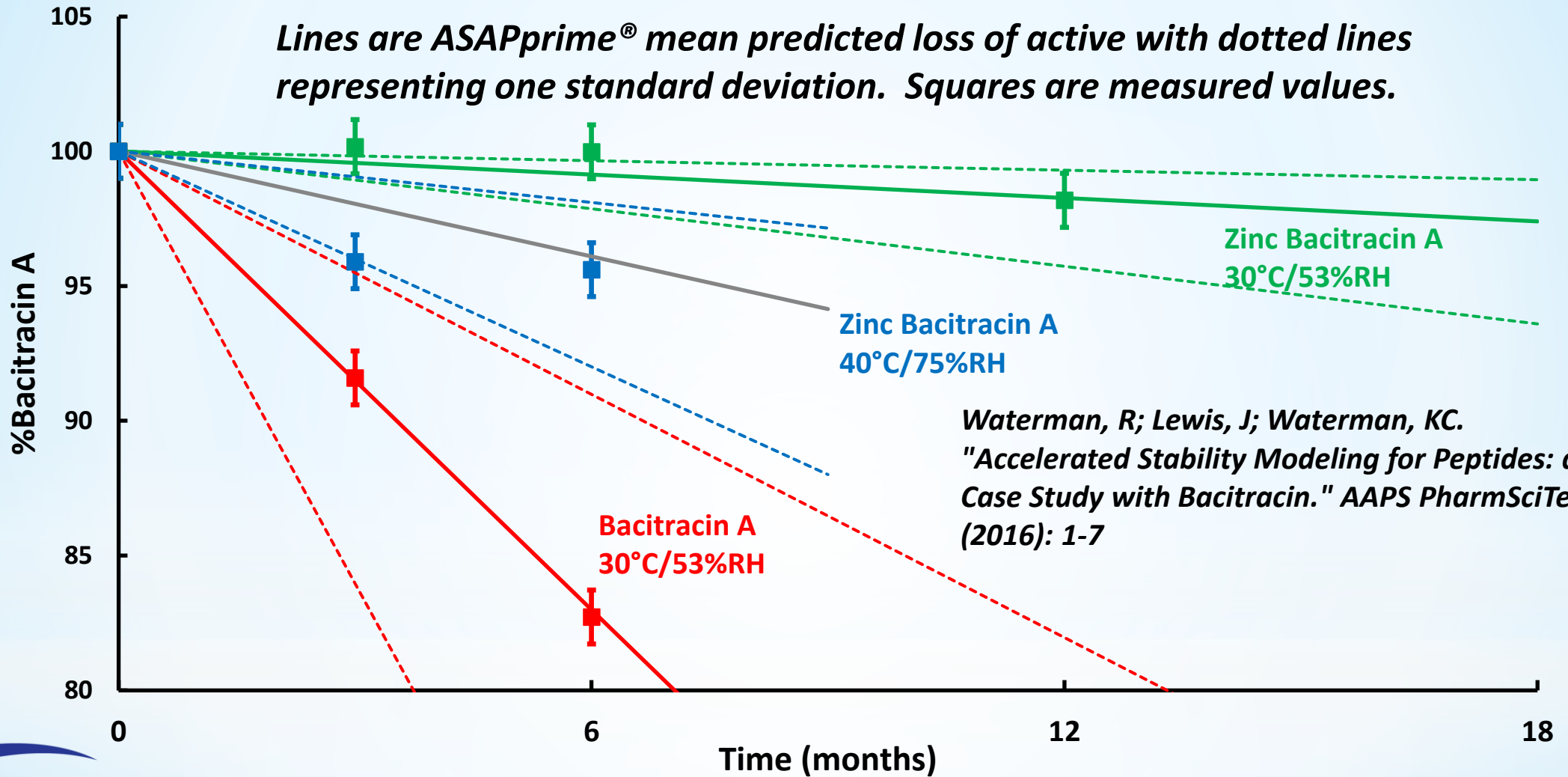
B = 0.02

Example 4—Nicorette[®] Lozenge

Condition (PVdC blisters)	Shelf-life (mos) <i>ASAPprime</i> [®] mean predicted	Shelf-life observed (mos)
25°C/60%RH	18	18
30°C/65%RH	7	8
30°C/75%RH	6	5
40°C/75%RH	1	1

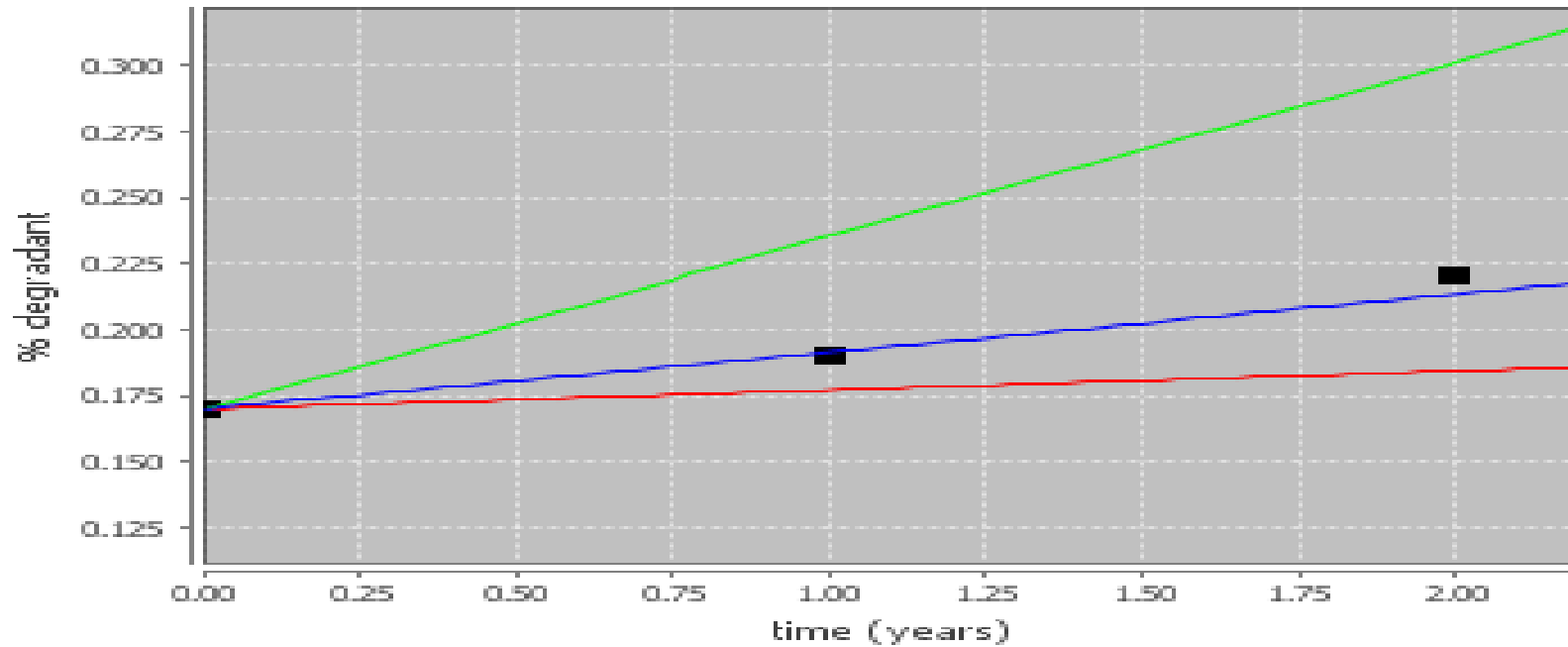
L. Chen, S. Faust, A. Venkatarangan (GSK Consumer Health) AAPS Poster 2013

Example 5: Peptide Stability



Example 6—75-cc HDPE bottles 25 capsules/bottle—Model vs. Measured

% degradant vs time (T = 25.0 ° C; RH = 60.0%)

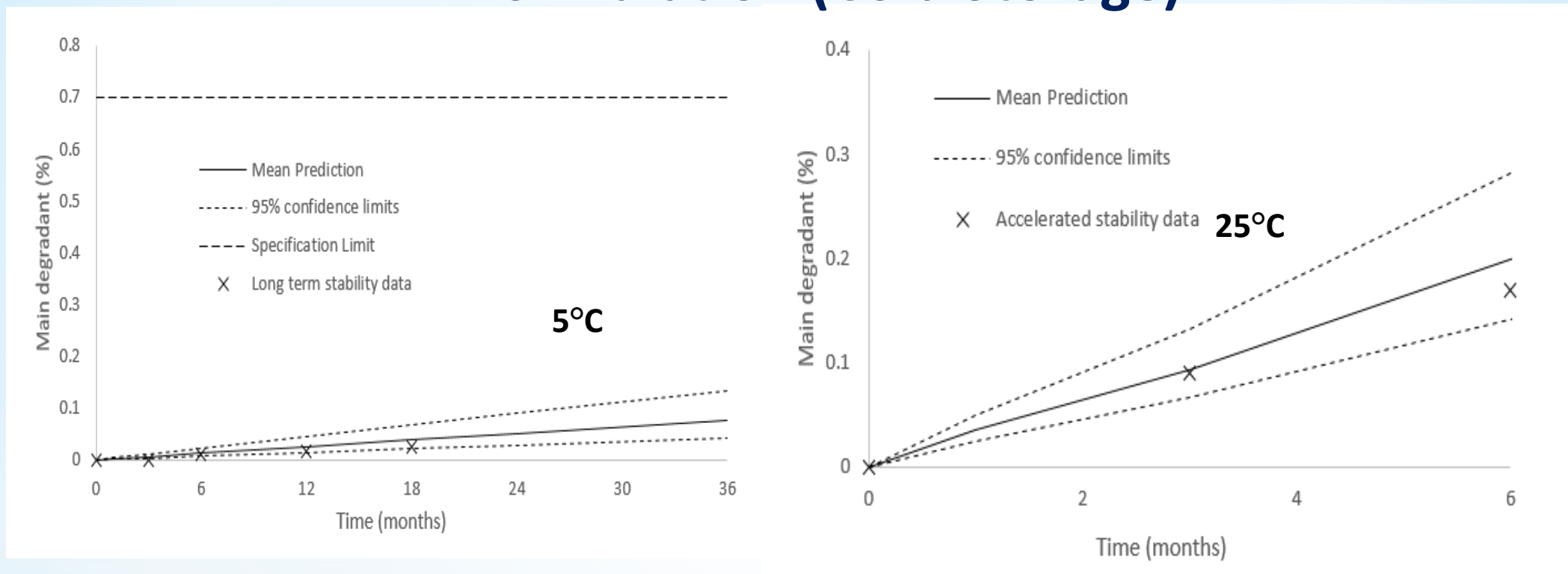


25°C/60%RH
#3 gelatin capsule

S. Thielges, Janssen 2013

Example 7

IV Formulation (Cold Storage)



*From H. Williams (Astra Zeneca) presentation
"Science of Stability Conference" Boston 2018*

More Examples

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

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

Future Additions to ASAPprime®: Staged Packaging



Operations:

- Switch from initial packaging to a “named” package (can be “open”)
- Change desiccant
 - Remove
 - Refresh
 - Add/increase amount
- Change number of dosage units
- Change storage conditions (equivalent to an excursion)

Future Additions to ASAPprime[®]: Staged Packaging

“Named” Package

Named Package

Name:

Add

Type

Delete

Vol (cc)

Material

Clear

Enter MVTR

MVTR (mg/day)	T (°C)	% RH

Accept **Cancel**

Future Additions to ASAPprime[®]: Staged Packaging

Change Package

Start Time
 days

New Package
 ▼

Change Desiccant

Start Time
 days

Remove
 Refresh
 Replace g

Change Dosage

Start Time
 days

Remove units
 Every days
For days

Future Additions to ASAPprime[®]: Staged Packaging

Staged Packaging

Packaging Stages

Time (days)	Operation	Details
30	Change Package	250 mL HDPE
60	Change Dosage	Remove 2 units

Add Stage **Change Package** ▼ **Modify Stage** **Delete** ▼

OK **Cancel**

Future Additions to ASAPprime®: KF Water

Sorption Isotherm (DVS) used in ASAPprime®

$$\%water_{DVS} = 100\% * \frac{water}{dry+bound}$$

Karl Fischer (KF) used with many regulatory filings

$$\%water_{KF} = 100\% * \frac{water+bound}{bound+dry+water}$$

ASAPprime® will:

- Allow users to set initial KF water level
- Plot KF water as a function of time in packaging

Future Additions to *ASAPprime*[®]: 21CFR Part 11 Compliance (Regulatory-friendly Additions)

Technically *ASAPprime*[®] does not fall under Part 11 compliance requirements (does not generate or store data....more of a fancy calculator), however...

- Password will be required when software started
- Login with different permissions:
 - Administrator
 - User
 - Reviewer
- Existing stored session will not be able to be overwritten
- Option to disable entry to degradant table except through csv file loading
- The program will provide options for customizing the signature block of the PDF report