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

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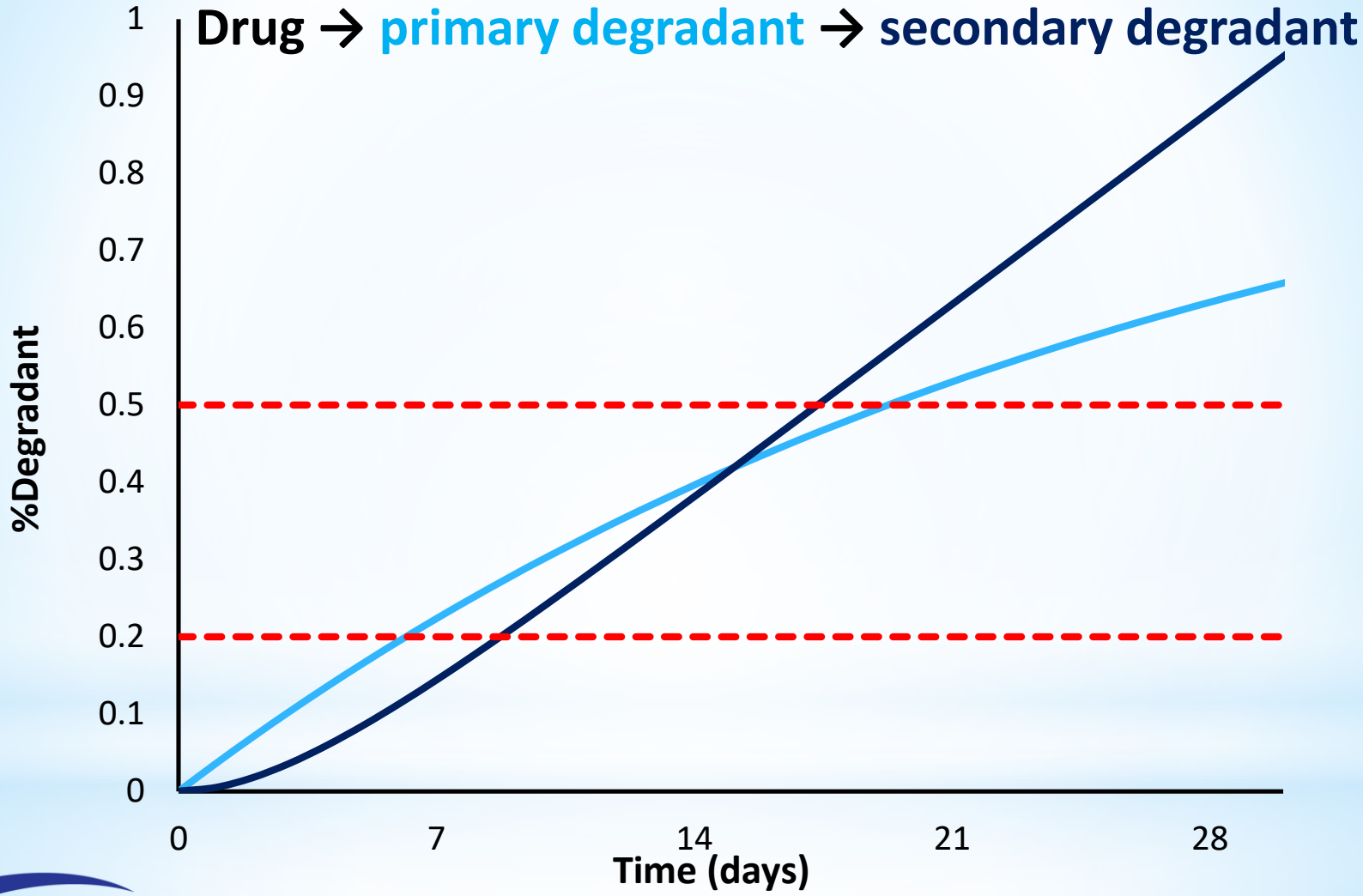
Outline

- **ASAP*prime*® 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



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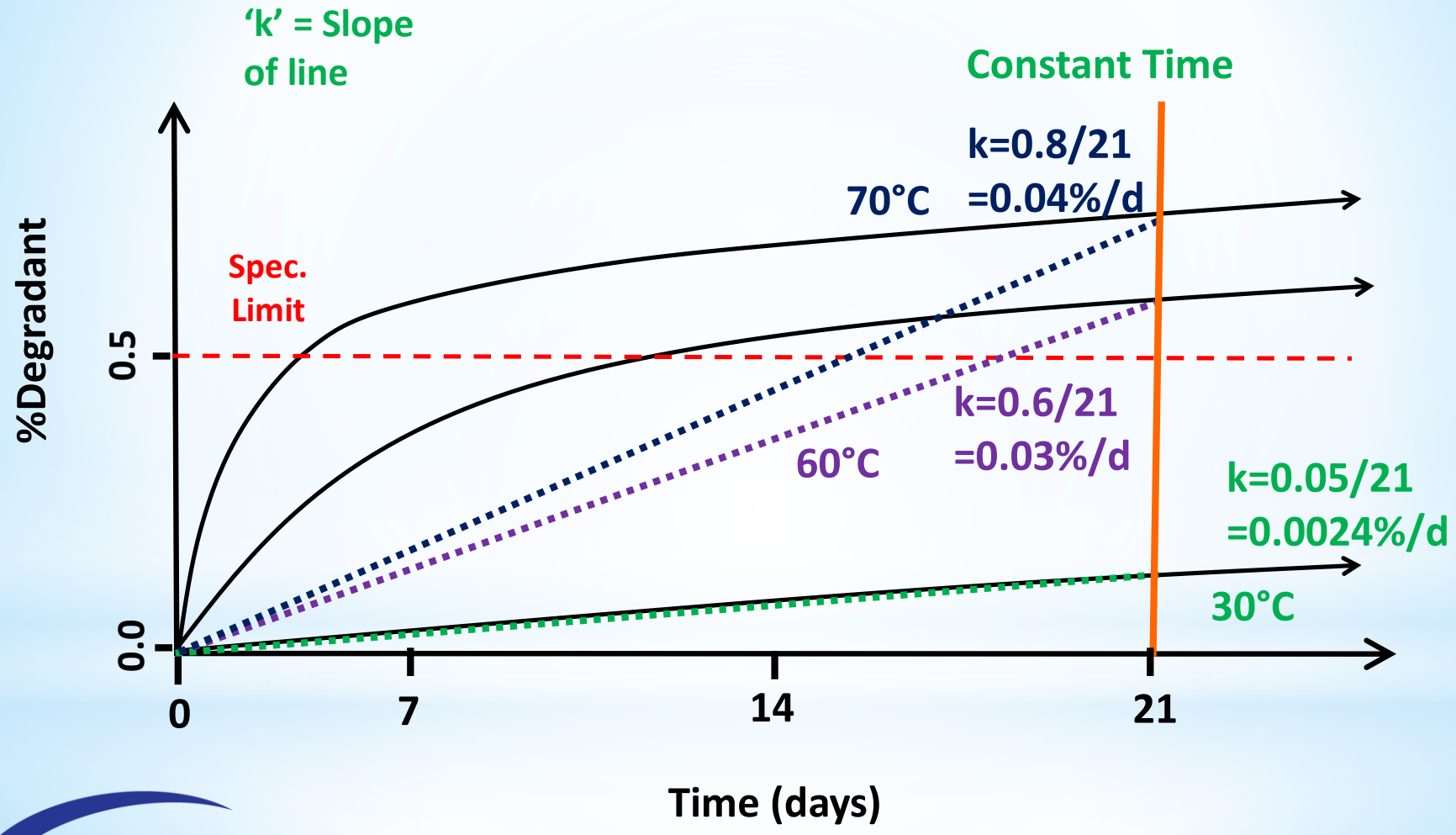
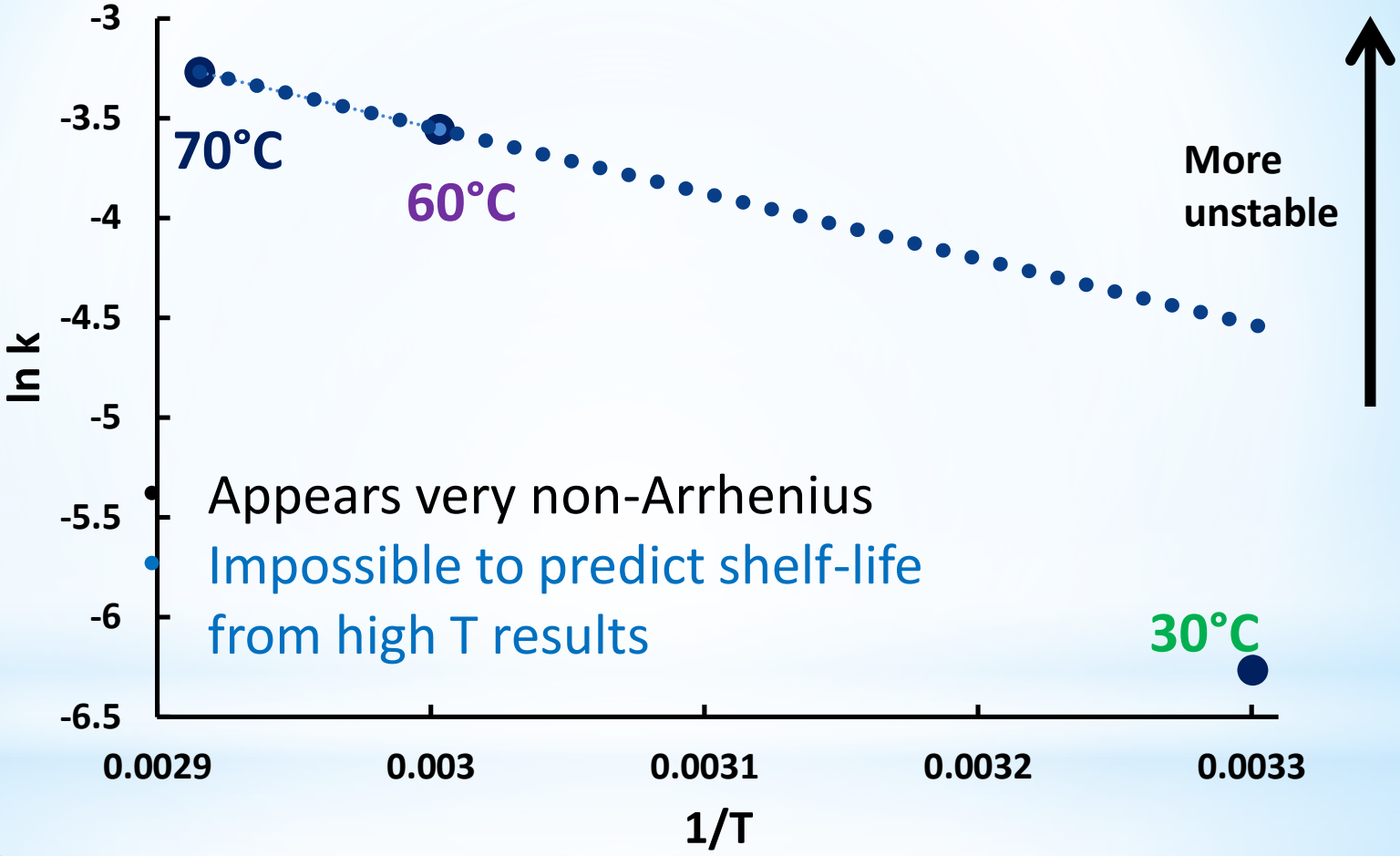
Traditional Accelerated Stability



Traditional Accelerated Stability



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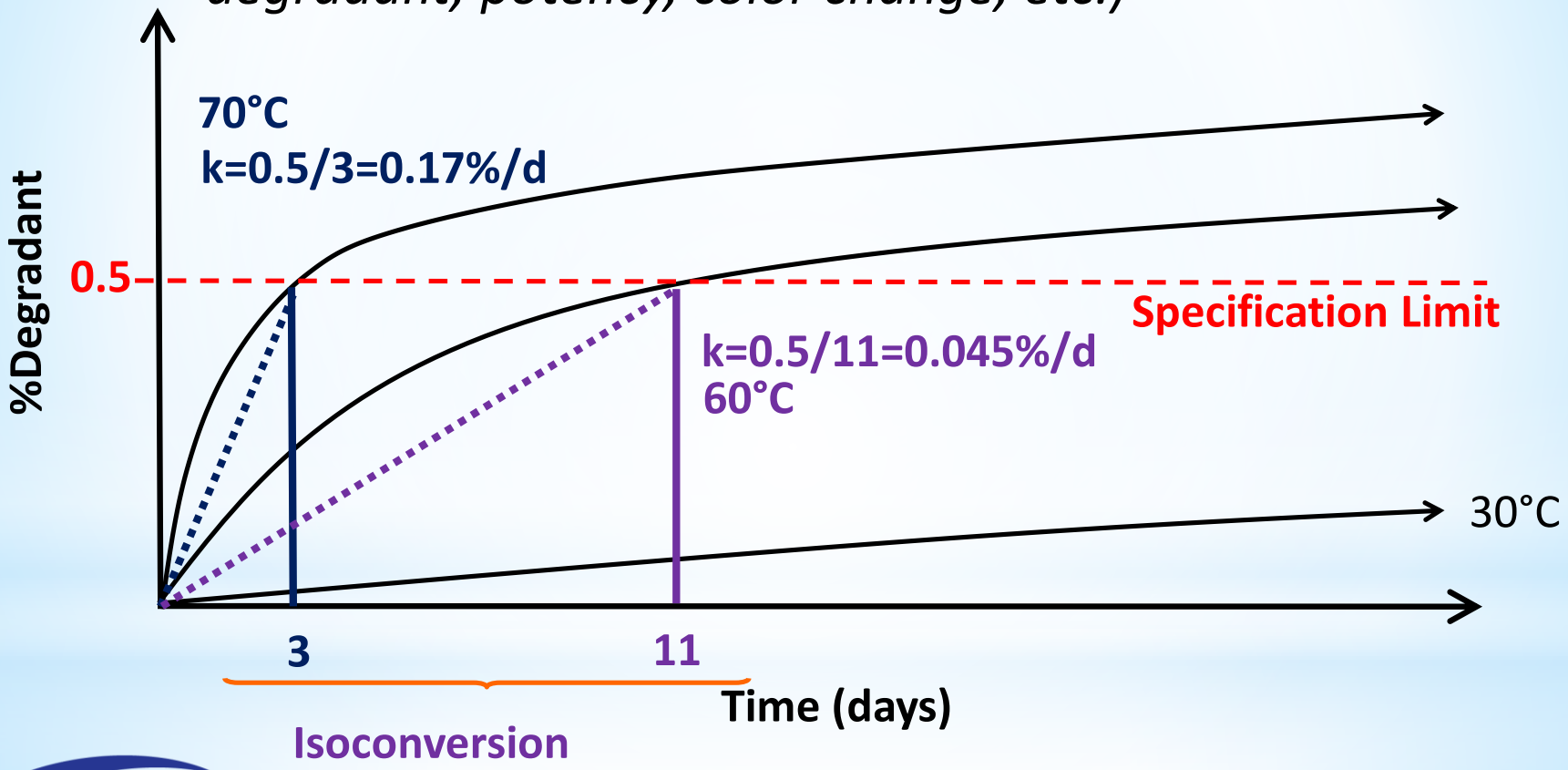
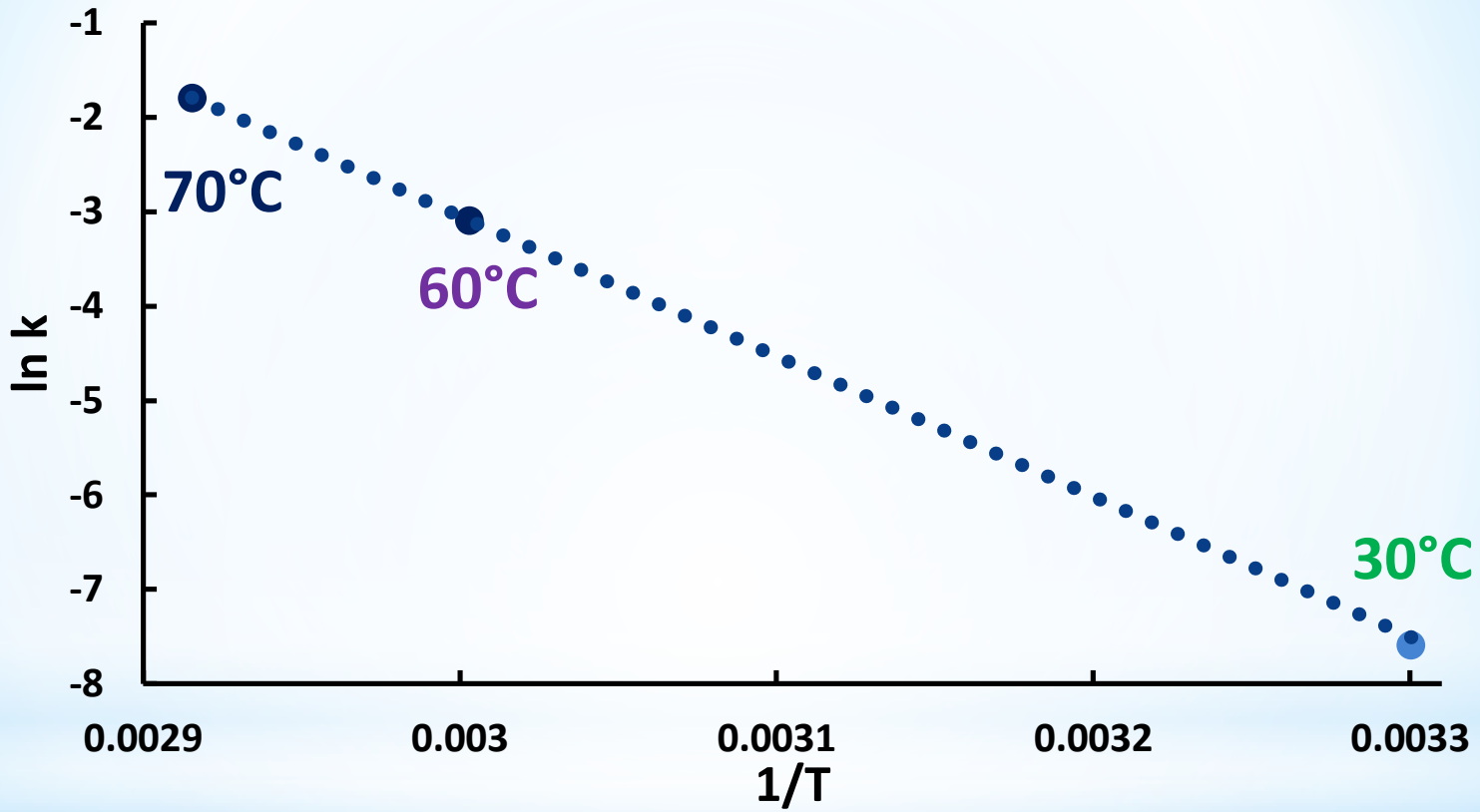
Isoconversion Accelerated Stability

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



Isoconversion Accelerated Stability



Accurate predictions do not depend on the kinetic form

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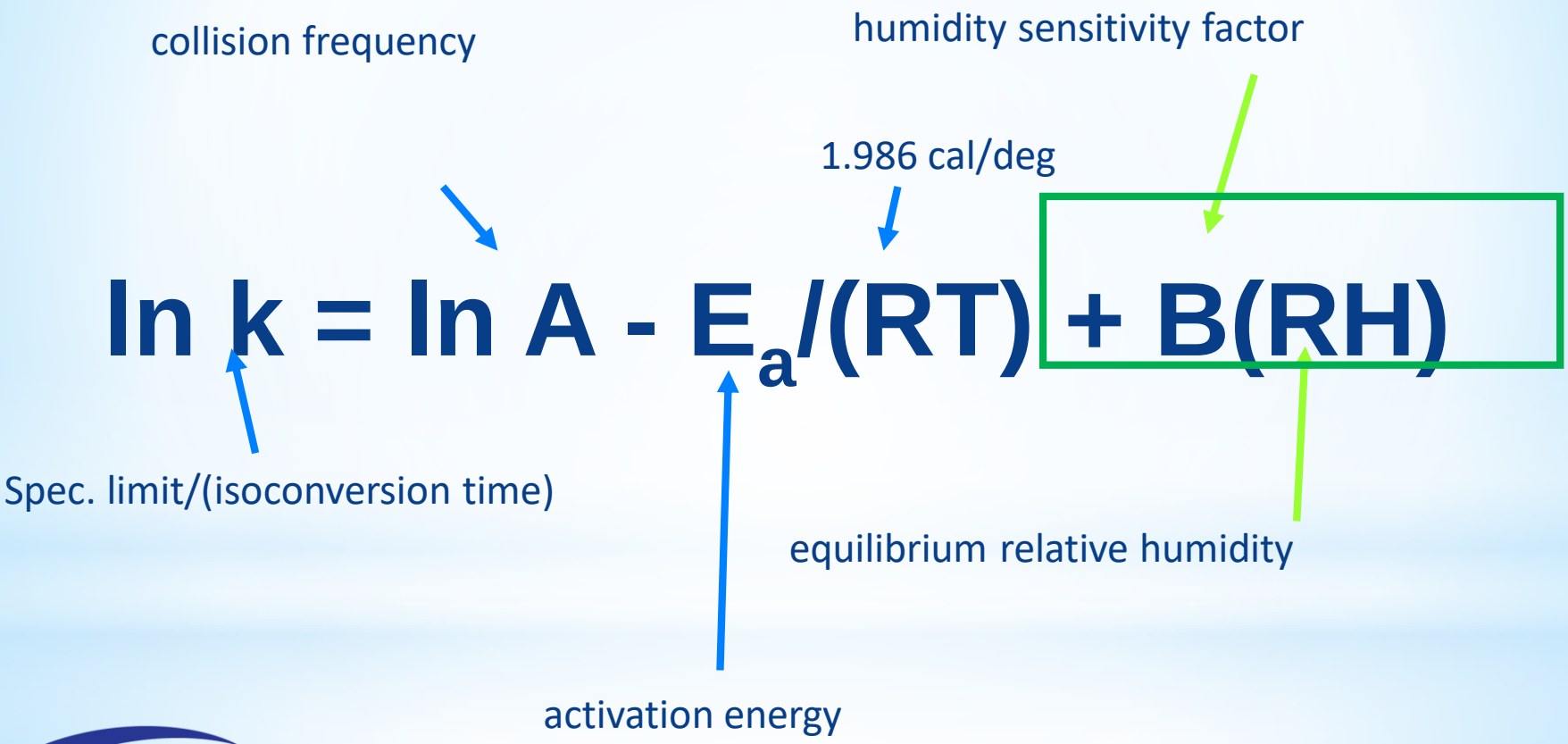
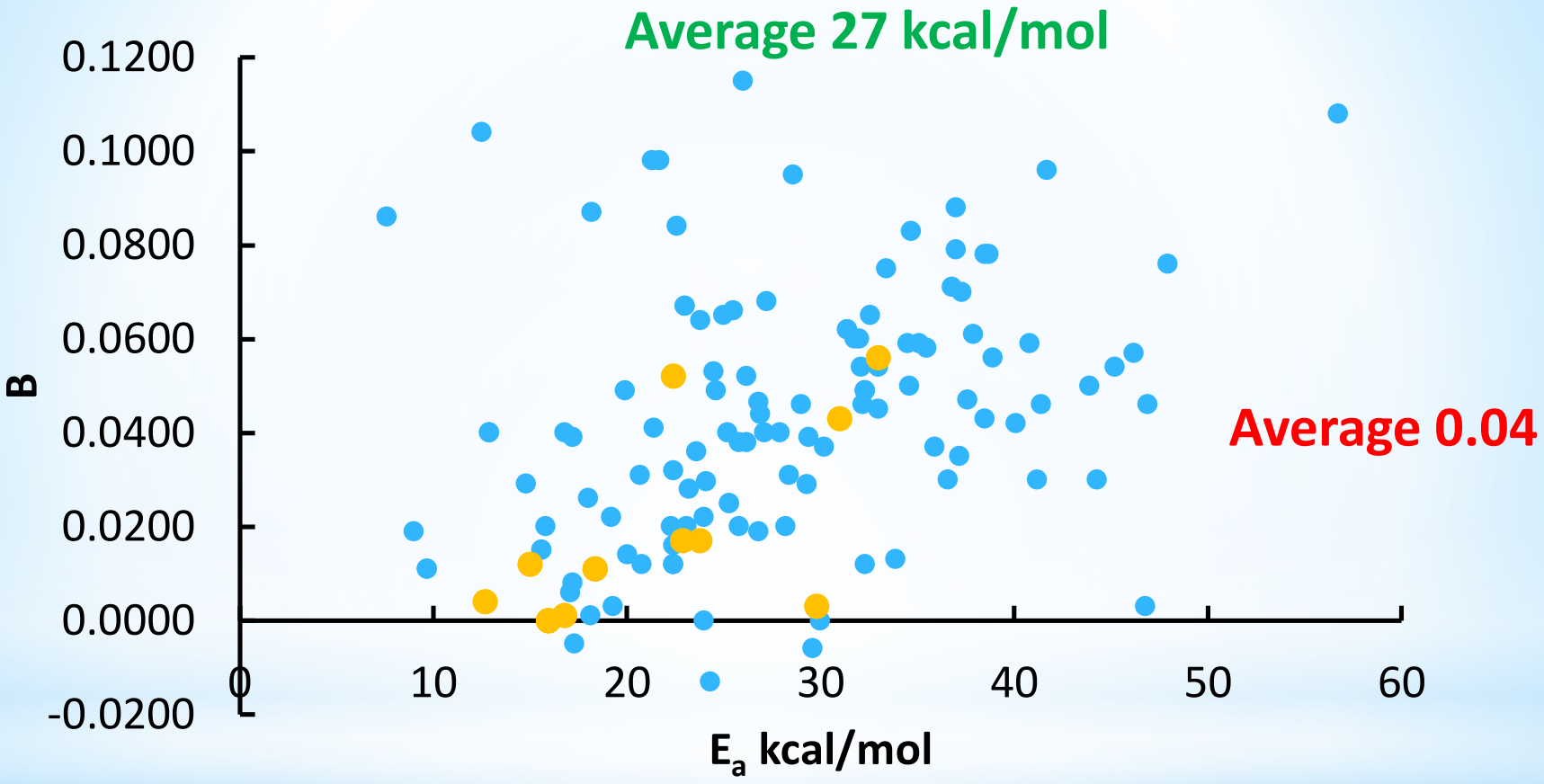
Humidity Corrected Arrhenius Equation



Typical E_a and B values
Drug Products and APIs Studied at FreeThink



RH sensitivity does not indicate hydrolysis!

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Impact of B Factor on Shelf-Life

B	60%RH in PVC Blister	65%RH in PVC Blister
0.00 **low moisture sensitivity**	5.0 yrs	5.0 yrs
0.04 **average moisture sensitivity**	5.0 yrs	3.8 yrs
0.09 **high moisture sensitivity**	5.0 yrs	3.0 yrs

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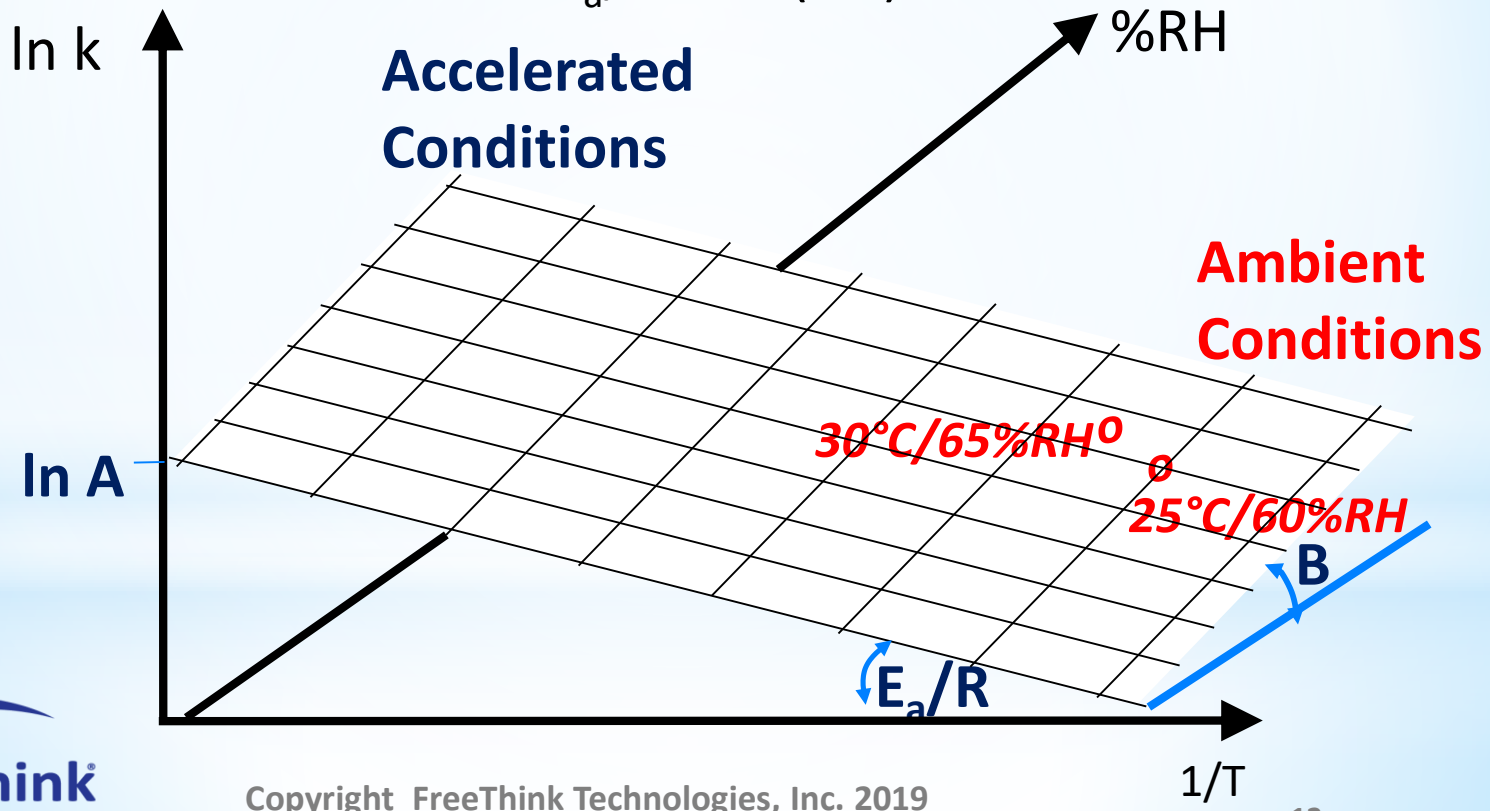
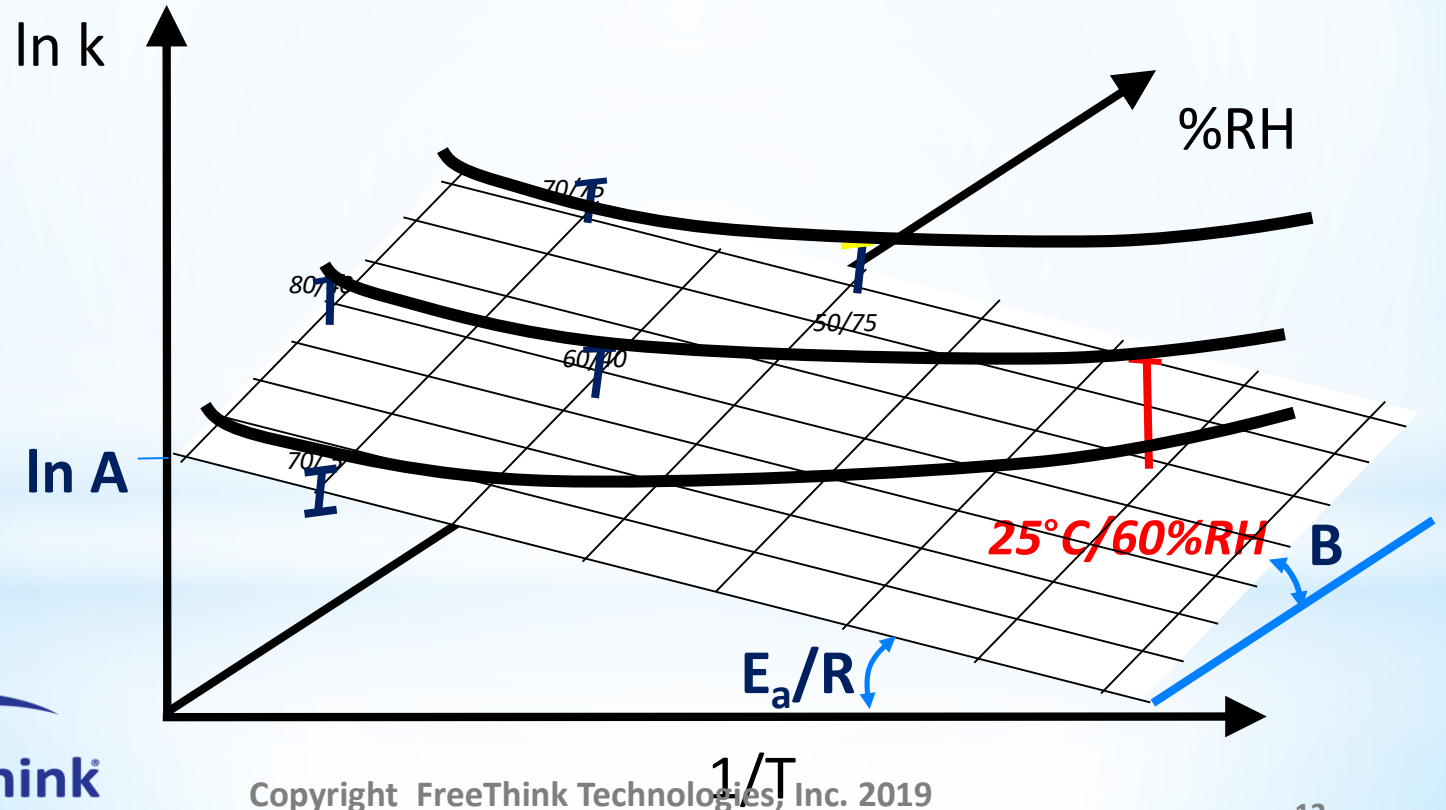
Accelerated Stability Assessment Program (ASAP) Design of Experiment: Determining the Plane

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



Error Bars

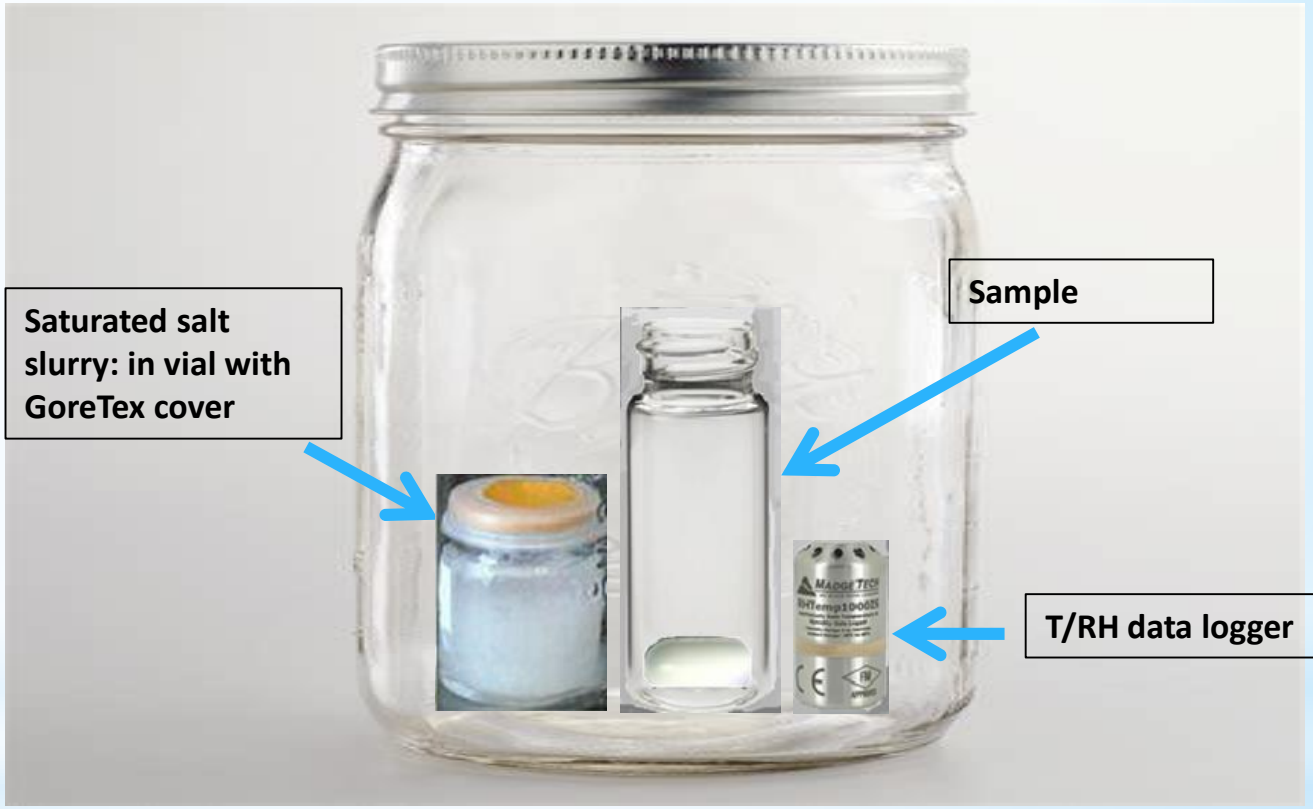
Estimation error bars increase with T extrapolation: fast stability studies (high T) are accurate, but lead to large error bars



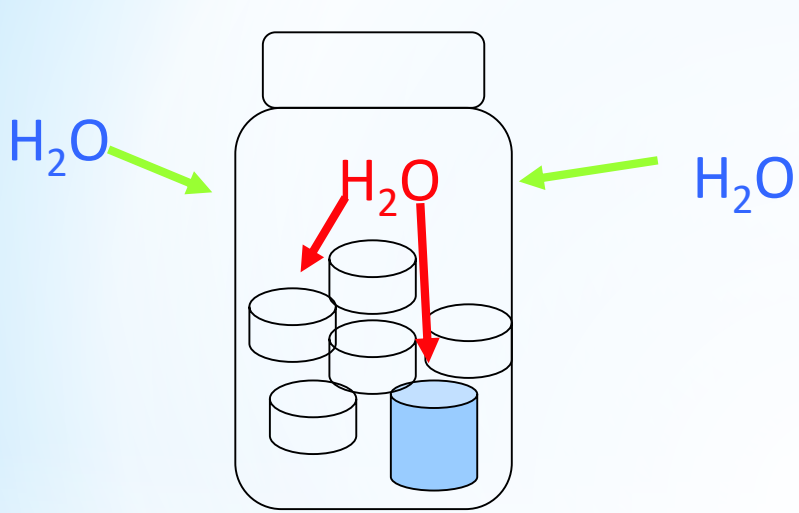
Experimental Setup

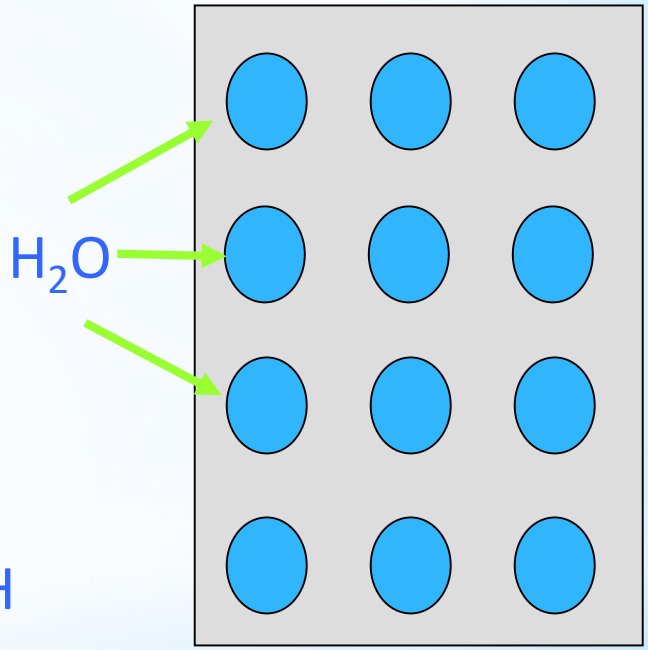
Mini-chambers:

Ball Mason jars
Hold seals even at 95°C



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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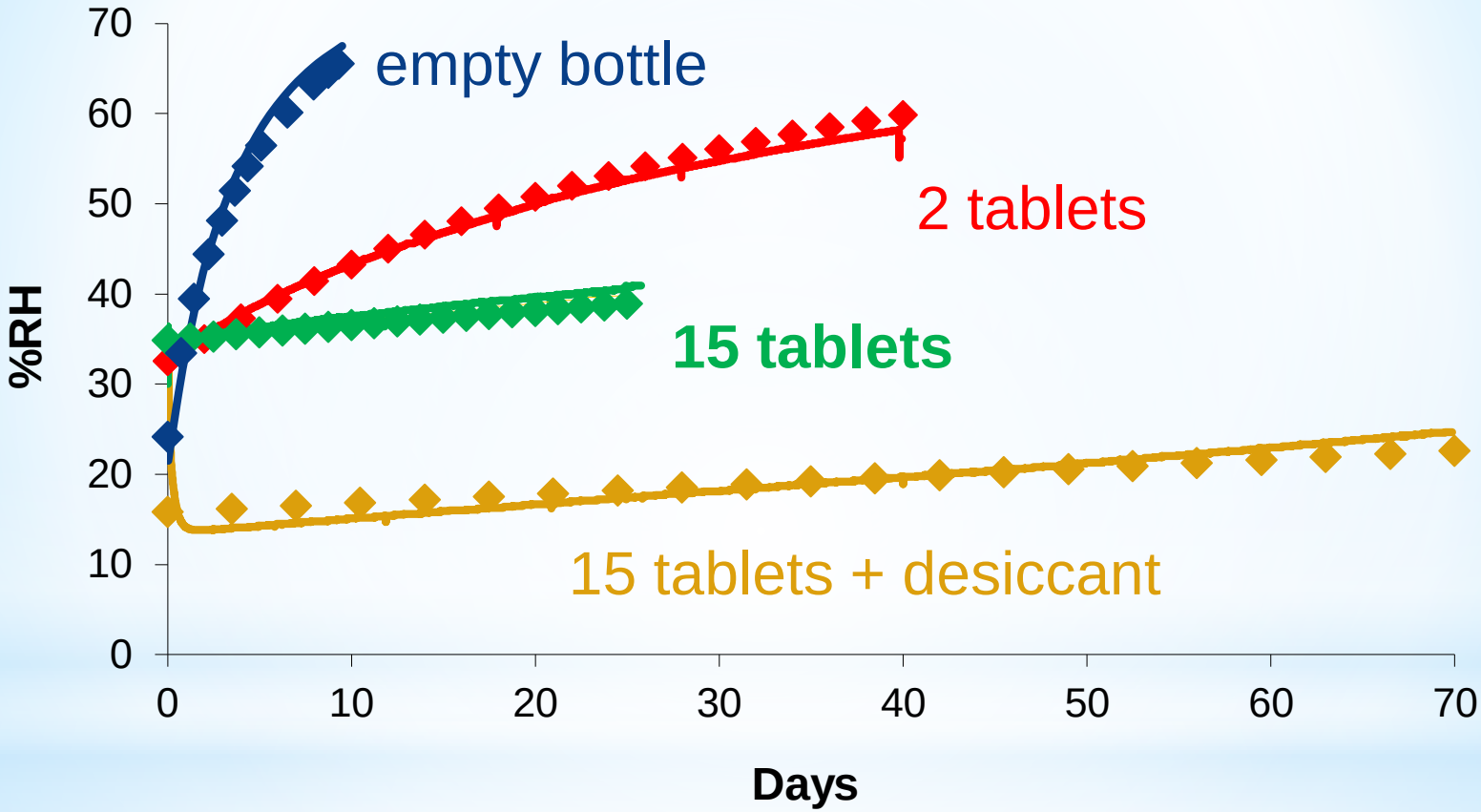
Relative Humidity as a Function of Time

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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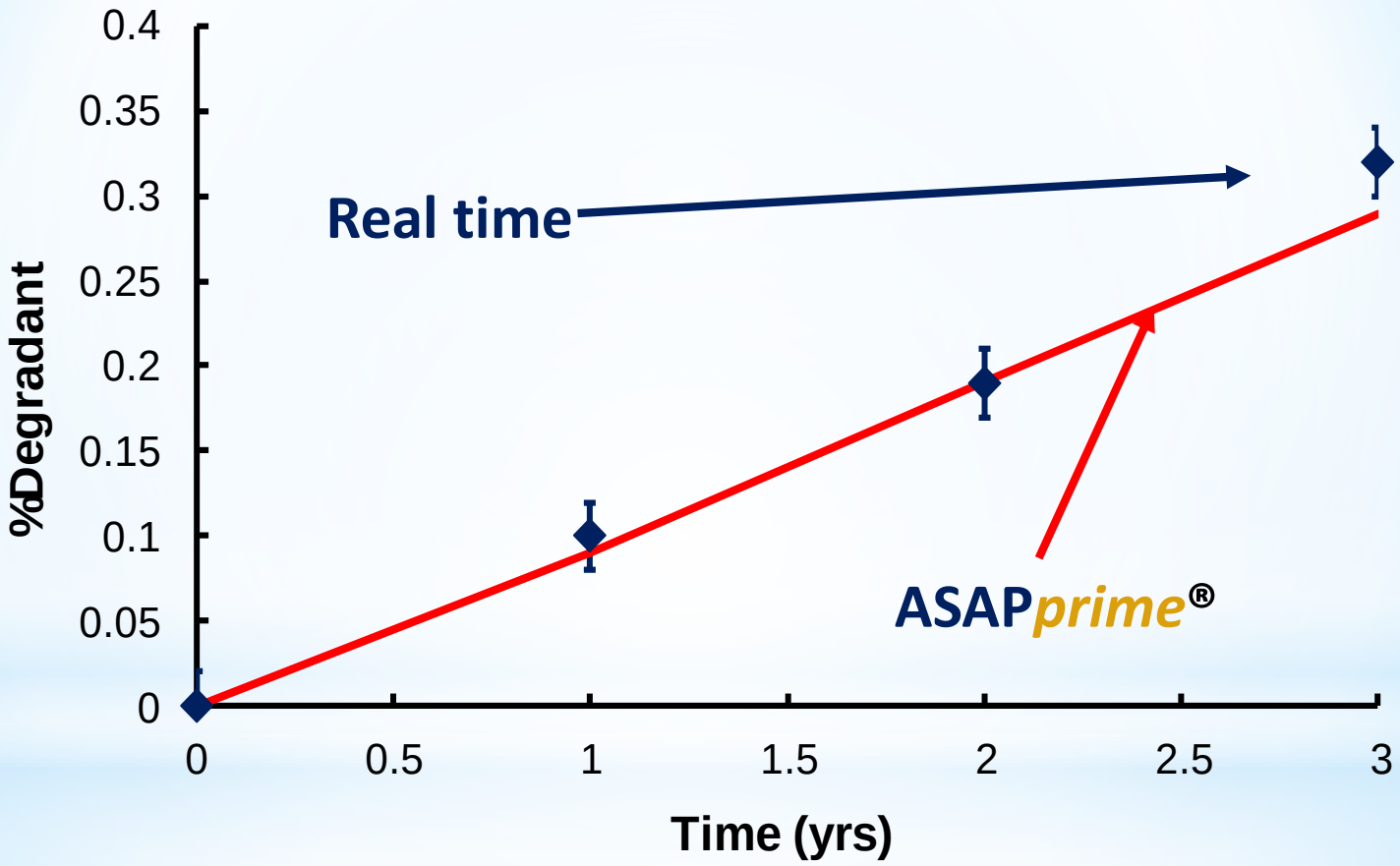
Example 1



Drug Product Tablets; 30°C/65%RH

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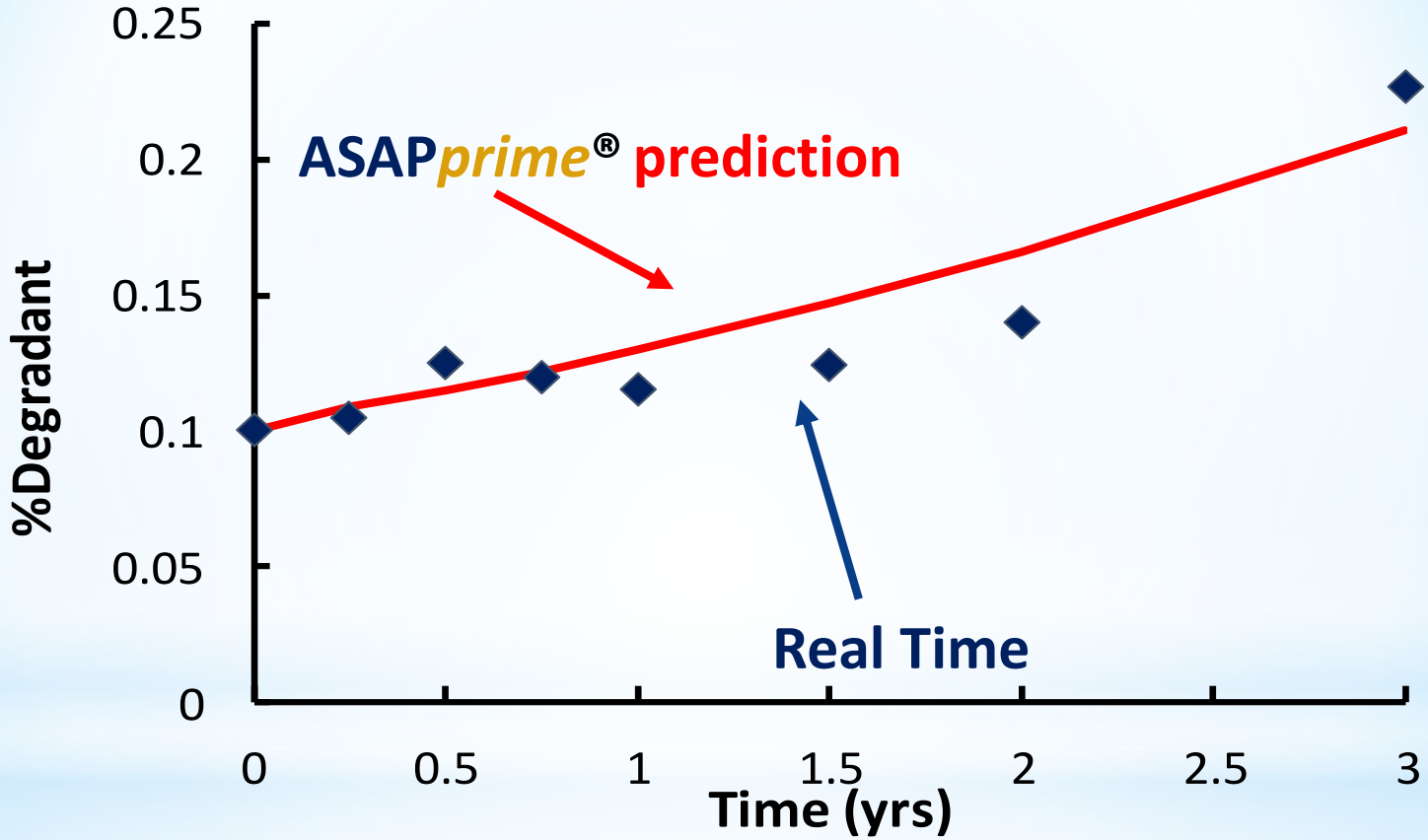
Example 2

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



B = 0.02

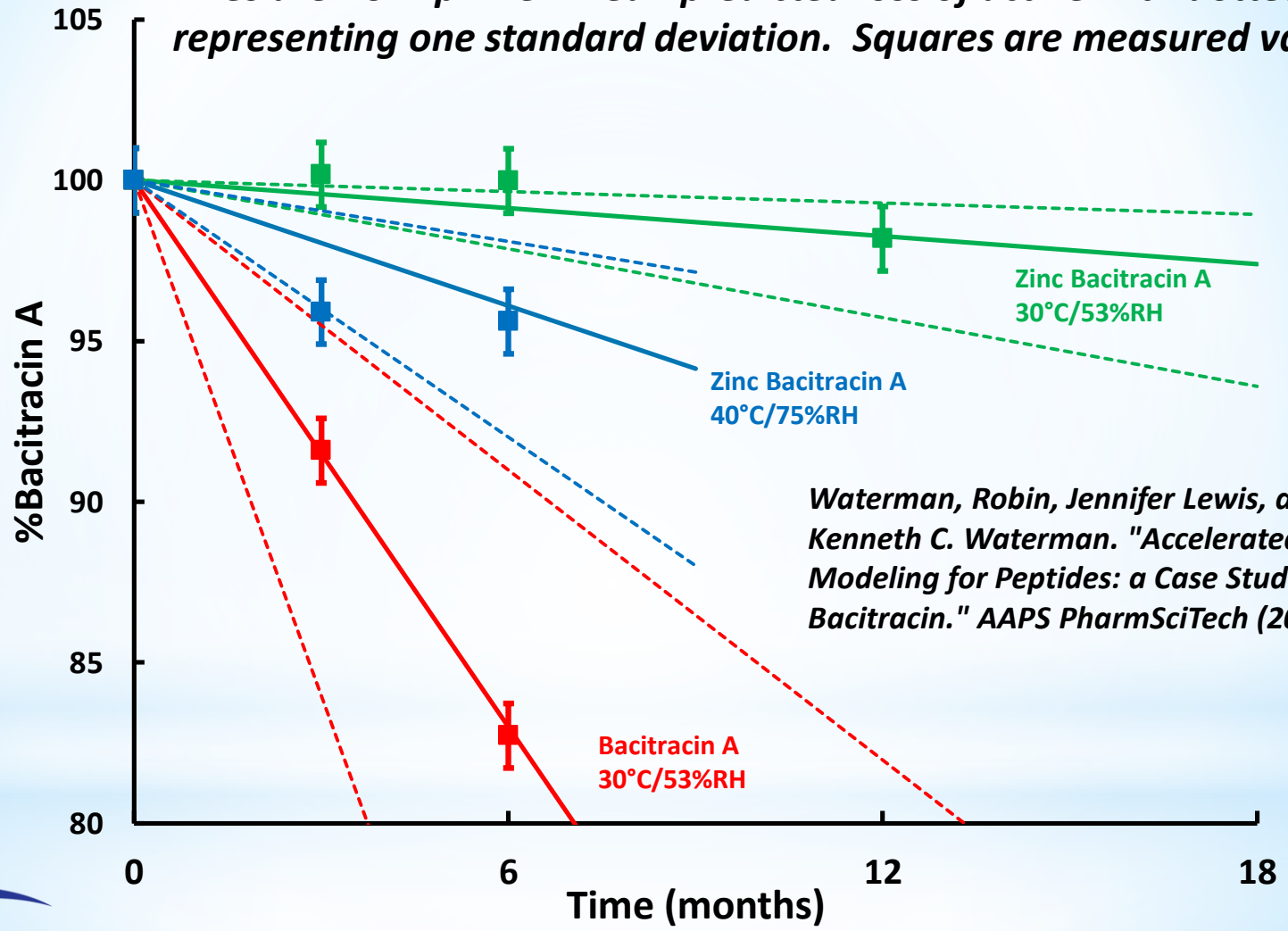
Example 3—Nicorette® Lozenge

Condition (PVdC blisters)	Shelf-life (mos) ASAP*prime*® 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 4: Peptide Stability

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



Waterman, Robin, Jennifer Lewis, and Kenneth C. Waterman. "Accelerated Stability Modeling for Peptides: a Case Study with Bacitracin." AAPS PharmSciTech (2016): 1-7

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Example 5: Formulation/Process Development

Tablet	E_a (kcal/mol)	B	%Probability of passing @2 yr, 30°C/65%RH
1	24	0.04	28
2	**29**	**0.06**	**88**
3	25	0.04	12
4	23	0.03	5
5	25	0.04	9

Tablet 2 was only one without wet-granulation. Program shifted to avoid water exposure of drug.

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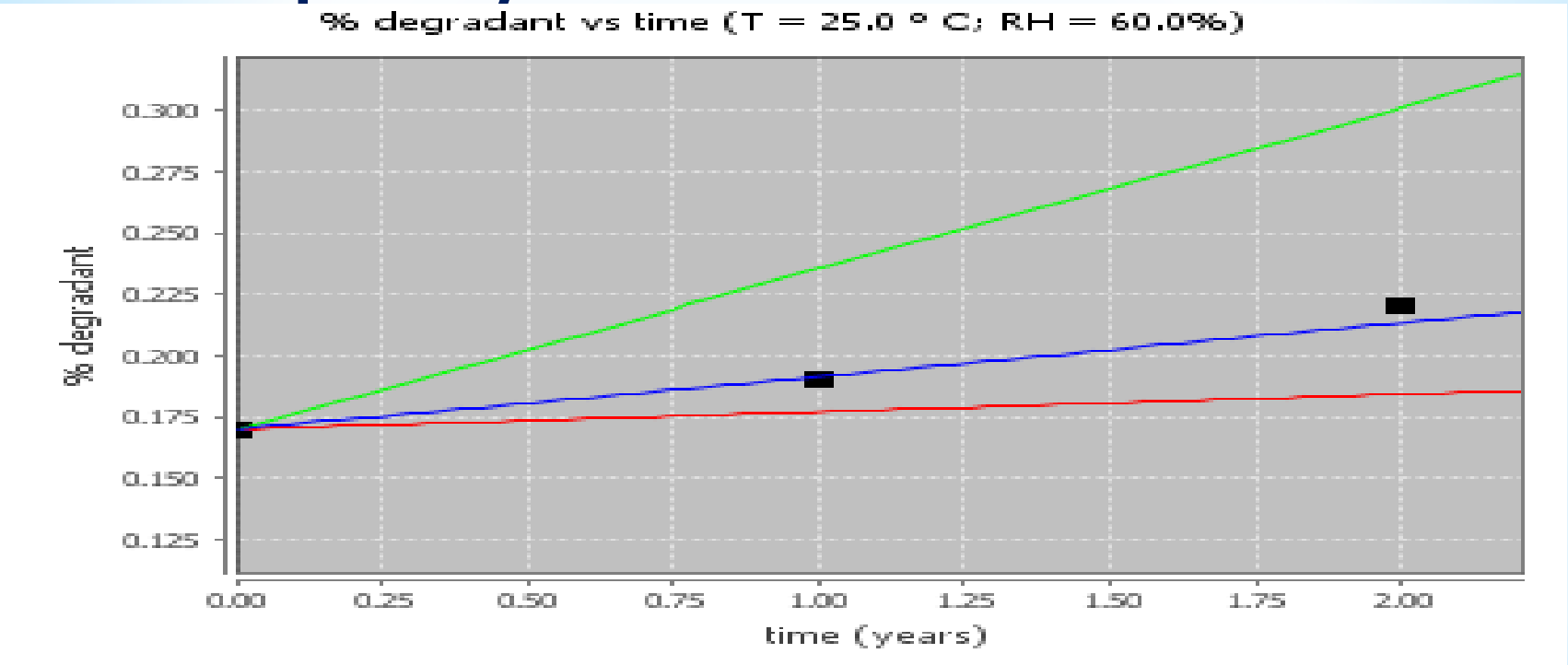
Example 6—75-cc HDPE bottles 25 capsules/bottle—Model vs. Measured

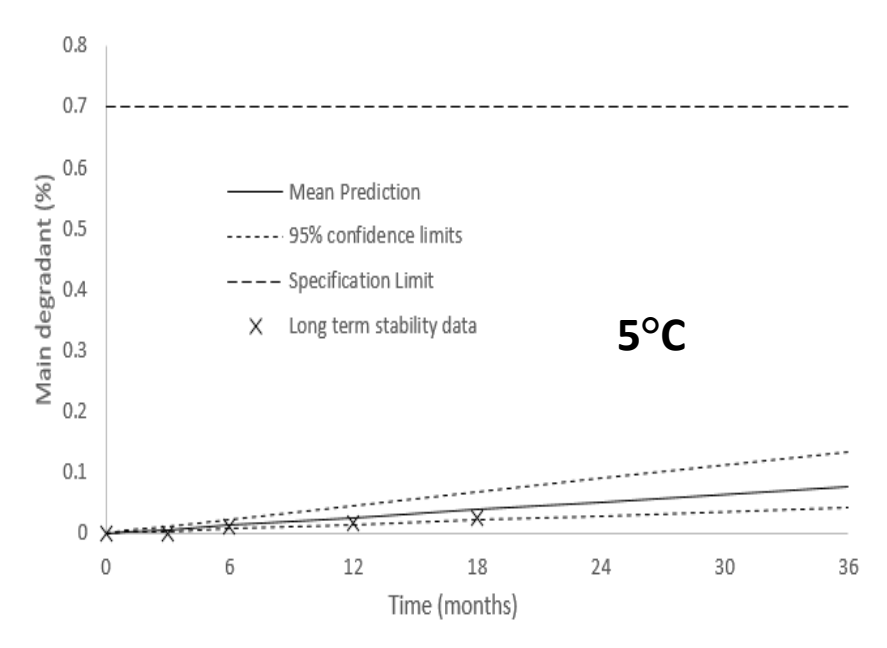


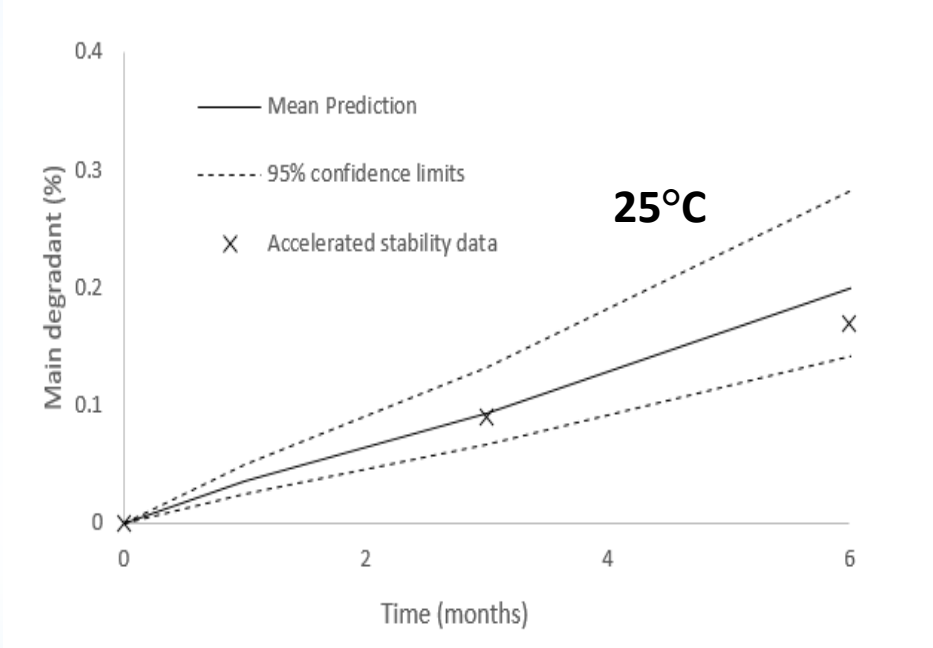
25°C/60%RH

#3 gelatin capsule

S. Thielges, Janssen 2013

Example 7
IV Formulation (Cold Storage)





From H. Williams presentation "Science of Stability Conference" Boston 2018

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More Examples

Product	Condition	ASAP*prime*®	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.)

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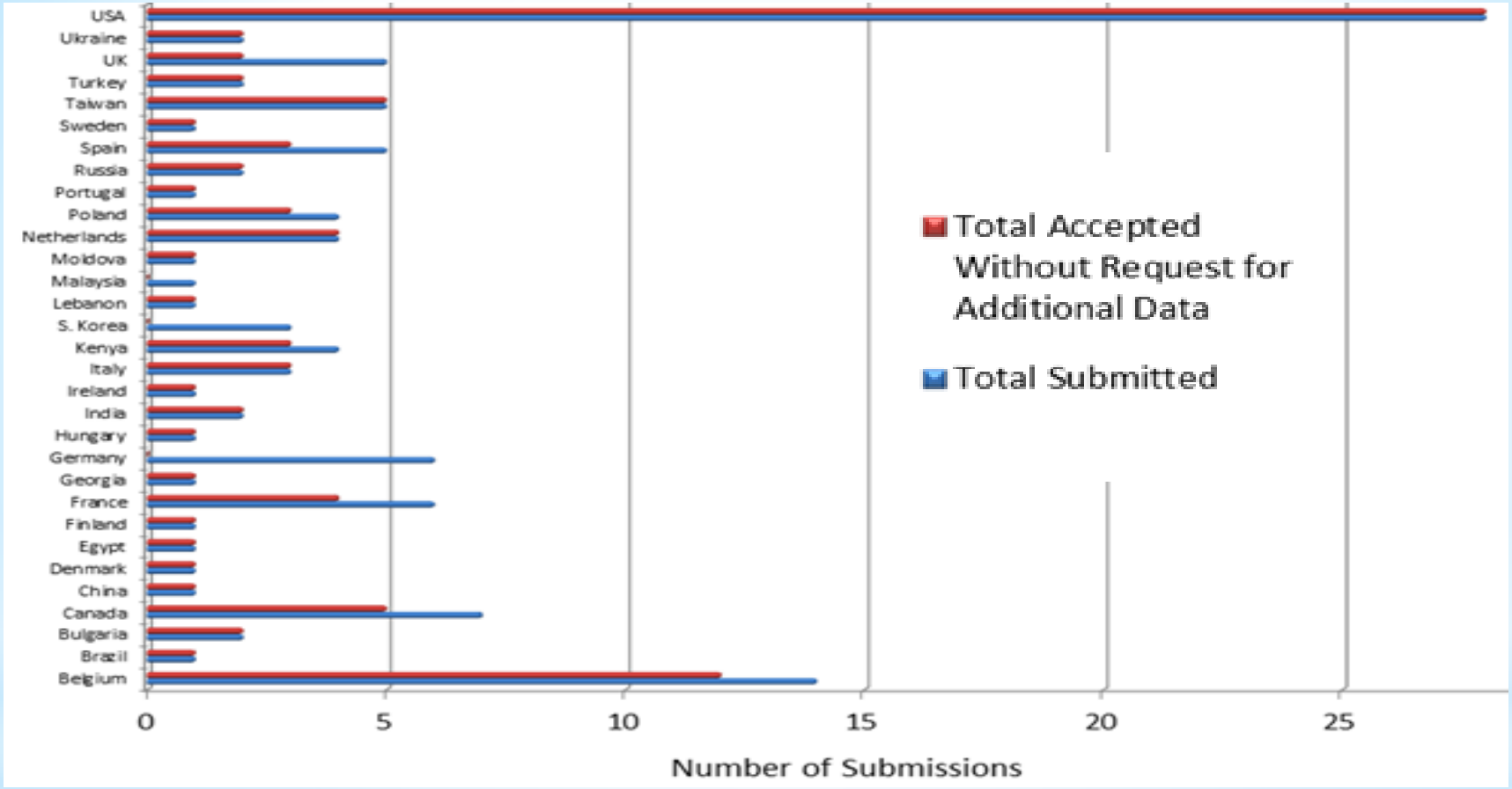
ASAP Regulatory Experience (Clinical) by Country



From F. Qiu presentation "Science of Stability Conference" Boston 2018

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Conclusions

- Accelerated stability can be applied effectively to set shelf-life with ASAP*prime*® using:
  - Isoconversion
  - Accounting for moisture sensitivity
  - Adapting statistics
- ASAP*prime*® enables better decisions, faster