Stability of Parenteral Drug Products

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Outline

- General Overview
- Small vs. Large Molecule Stability
  - Small molecules
  - Proteins
- Small molecule chemistry
- Protein stability issues
- Packaging
- Accelerating Degradation
- Conclusions

Background

- Marketed pharmaceutical products need to specify shelf-life under storage conditions
  - Assure safety
  - Assure potency/activity
  - Have no obvious visual changes
    - Precipitation
    - Discoloration
- **Shelf-life set by what hits its limit first!**

ICH Climatic Zones

Zone	Climate	Temperature	%RH
I	Temperate	21°C	45%
II	Subtropical	25°C	60%
III	Hot dry	30°C	35%
IVa	Hot, humid	30°C	65%
IVb	Hot, very humid	30°C	75%

Many parenterals are stored refrigerated: 5-8°C

Safety

- Degradation products of a drug are a potential safety risk
- Lower risk if degradants identified
    - Metabolites generally low risk
    - Qualification of degradants based on defaults (typically 0.2-0.5% of active) or safety data
    - Compounds with genotoxic risk are more tightly regulated
- **Microbial count needs to remain acceptable at end of shelf-life**
    - **Monitor preservative levels**

Potency

- Drug product needs to remain active at the end of its shelf-life (typically, >85% of label claim)
  - Loss of activity can be due to physical changes, e.g., precipitation
  - Loss can be due to chemical degradation
- Variability can play big role (may have differences between unit doses)

Small Molecule vs. Protein Stability

Small Molecules

- Loss of potency by any molecular change
- Only concerned with primary structure
- Most shelf-life limited by formation of low levels of degradants
- Arrhenius behavior in solution; modified Arrhenius (***ASAP***) in solid

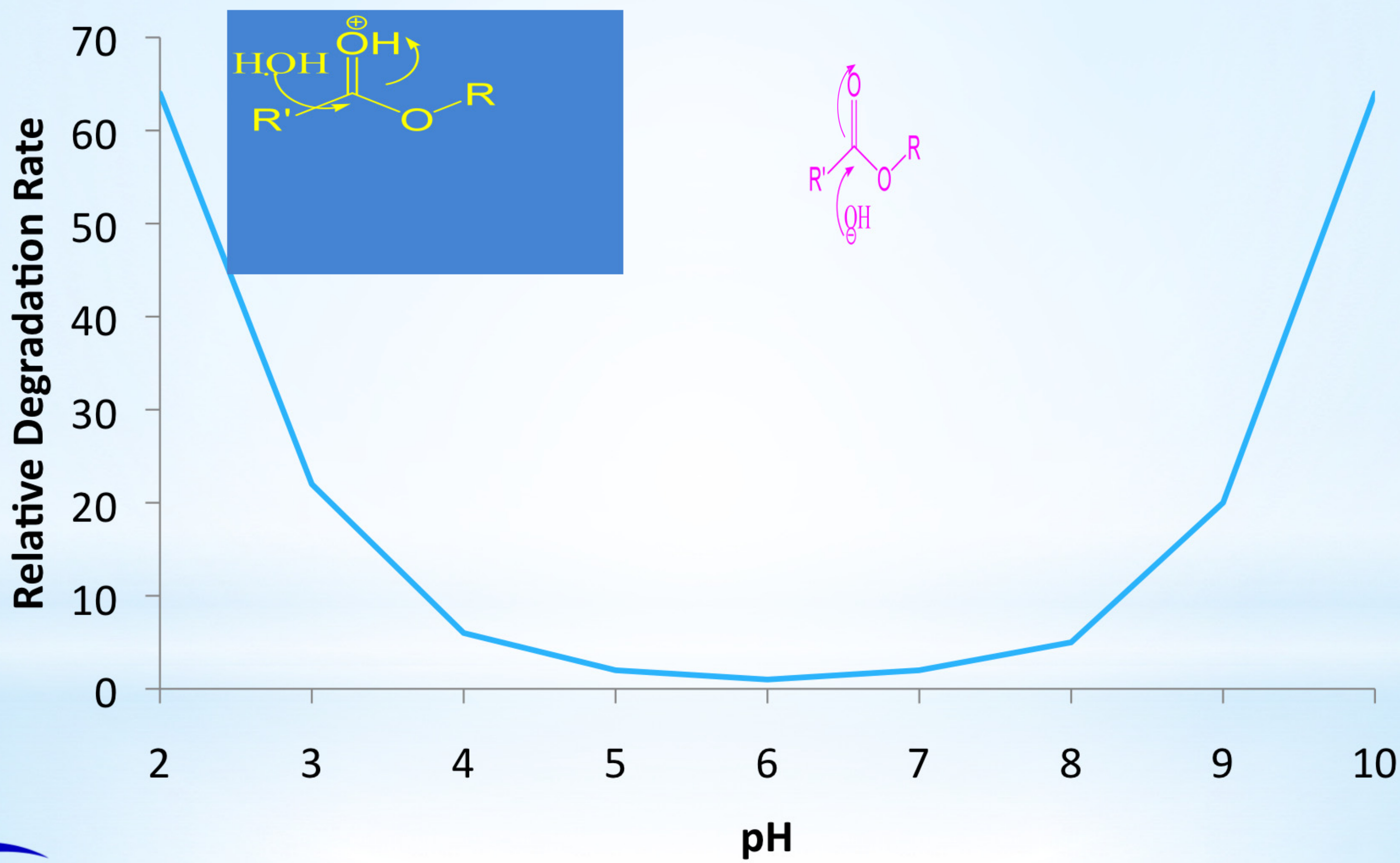
Proteins

- Some bond changes may not impact activity
- Small changes in structure can have a large impact on activity
- Concerned with 1°, 2°, 3° and 4° structures
- Multiple reversible and irreversible steps make Arrhenius behavior difficult to see even in solution

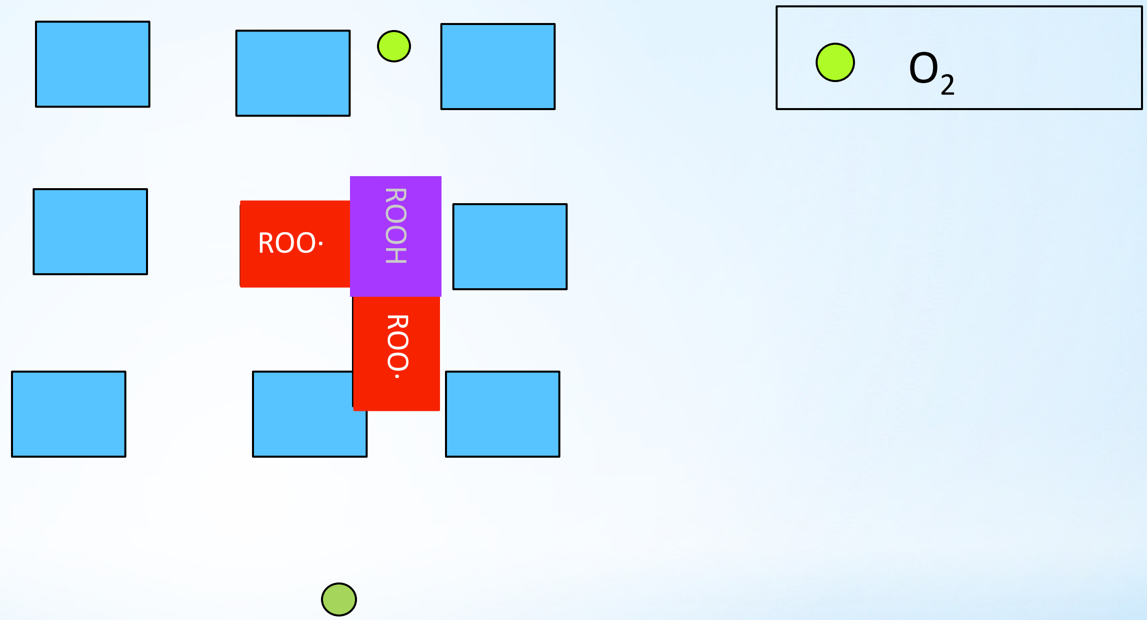
Small Molecule Degradation Chemistry

- Hydrolysis
  - Esters, amides
- Oxidation
  - Amines, sulfides
- Reaction with excipients, impurities
  - Maillard (amines + sugars), reactions with peroxides, formaldehyde
- Rearrangements
  - Lactonization, lactamization

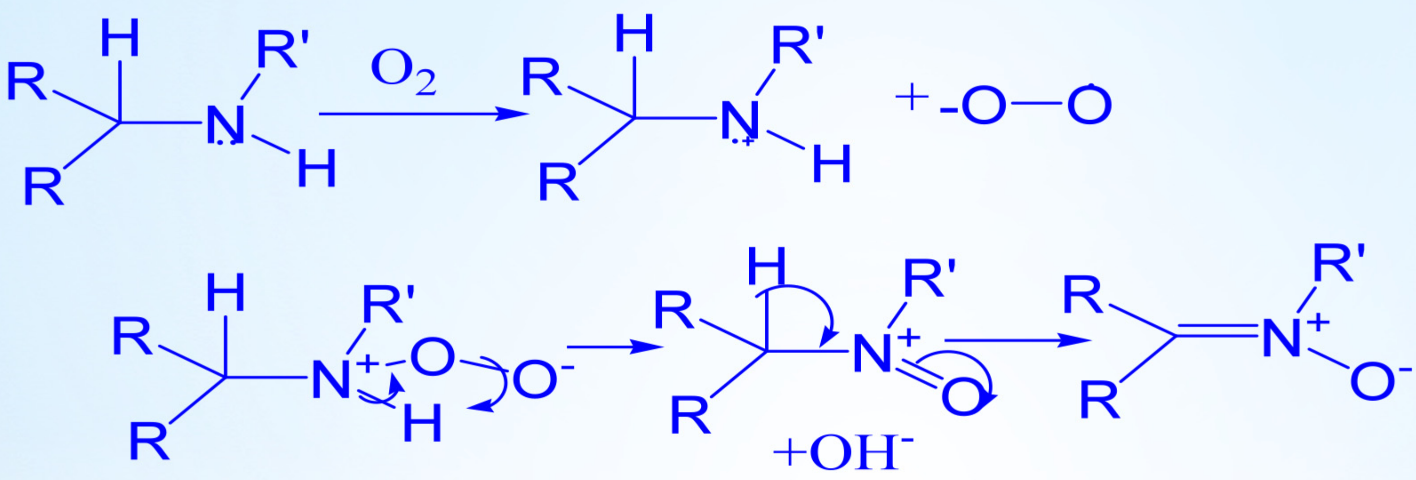
Hydrolyses Generally pH-Dependent



Oxidation: Classic Reaction with Oxygen



Oxidation of Electron-Rich Species



Oxidation slower at low pH

Antioxidants

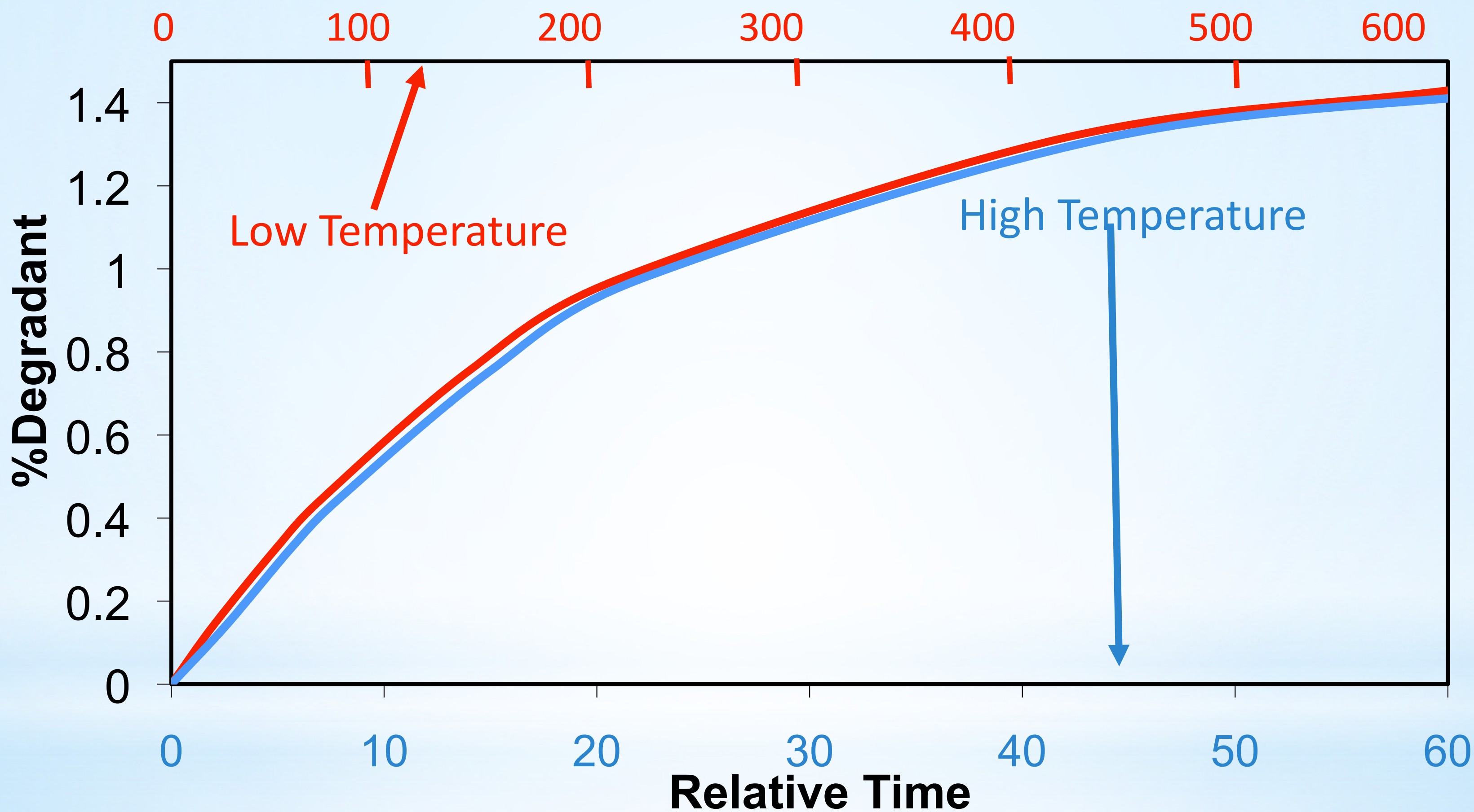
- Oxidations can be controlled by antioxidants (e.g., BHT, BHA)
- Oxidation can be fast once antioxidant is consumed
  - Need to monitor antioxidant levels with time

Accelerated Aging: Small Molecule Solutions

- Chemical Stability (Including Antioxidants/Preservatives)
  - Generally follows Arrhenius behavior
  - Temperatures close to 100°C have low oxygen and may not be predictive
  - Change in pH with temperature may need to be accounted for

- Physical Stability
  - Precipitation can be accelerated using heat cycling
  - Loss of stabilizers to diffusion into packaging generally follows Arrhenius behavior, but complicated by solubility changes with temperature

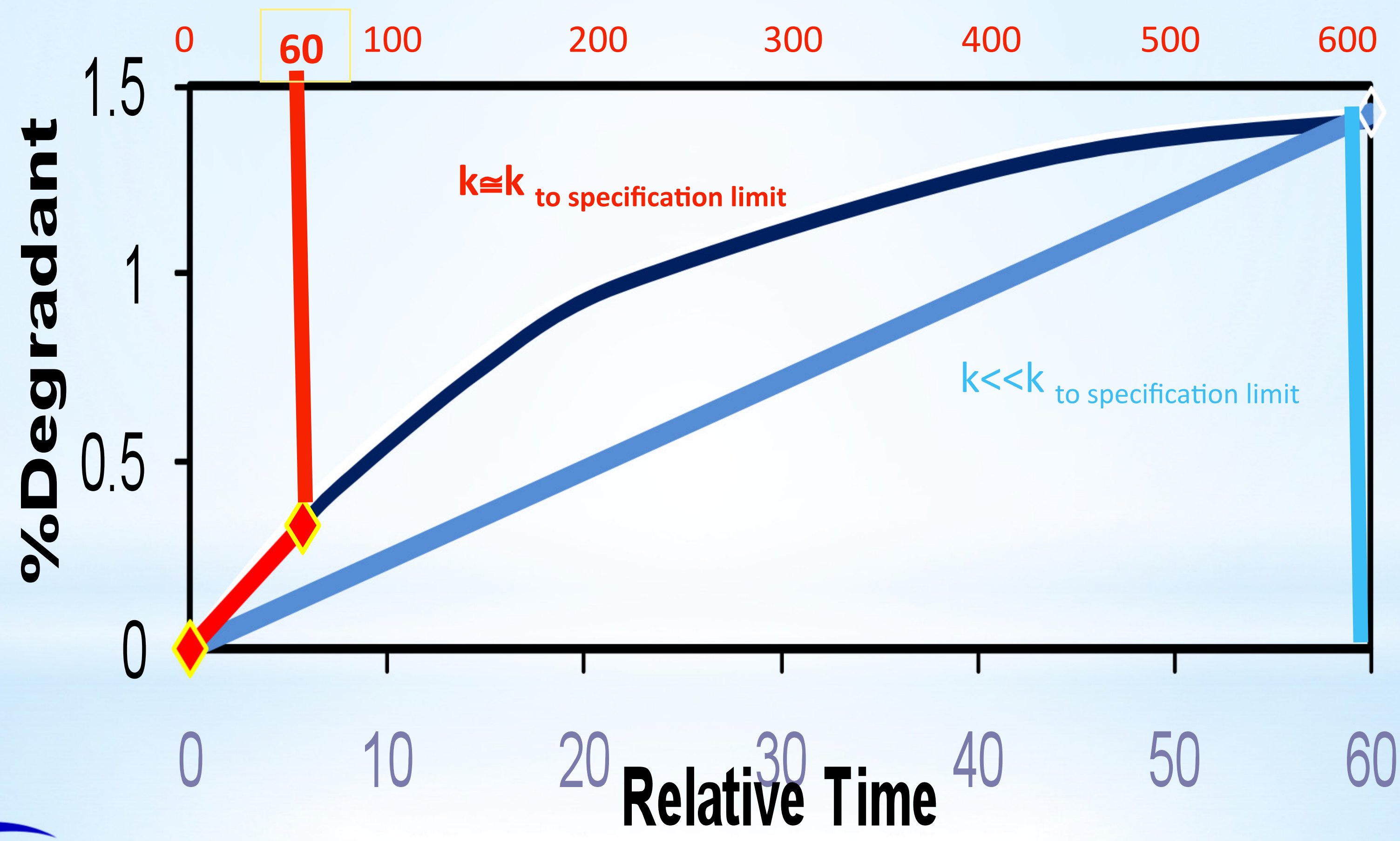
Small Molecule Accelerated Stability



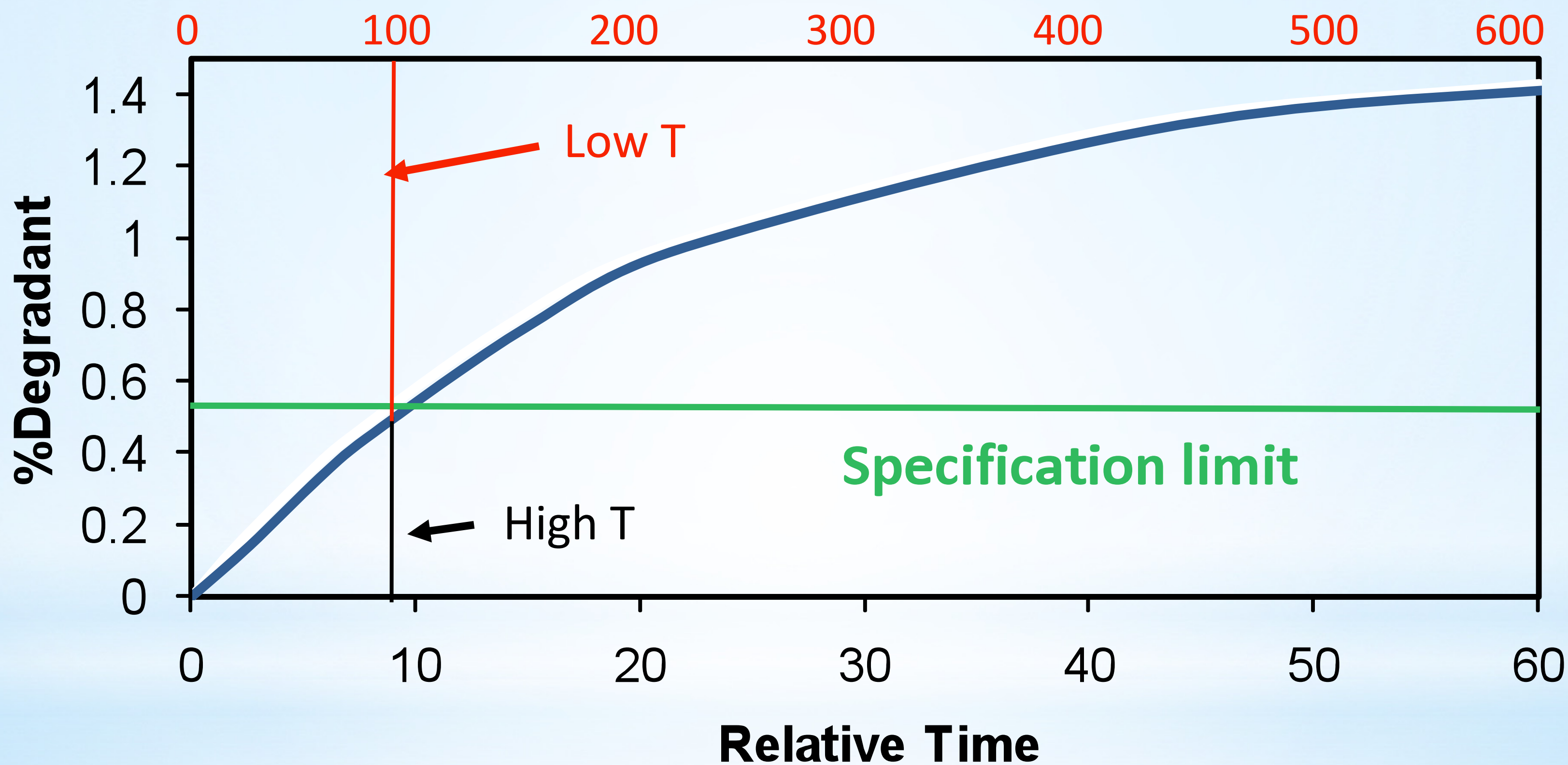
Same curvature independent of T

Accelerated Stability: Traditional Approach

60 Days at low or high T

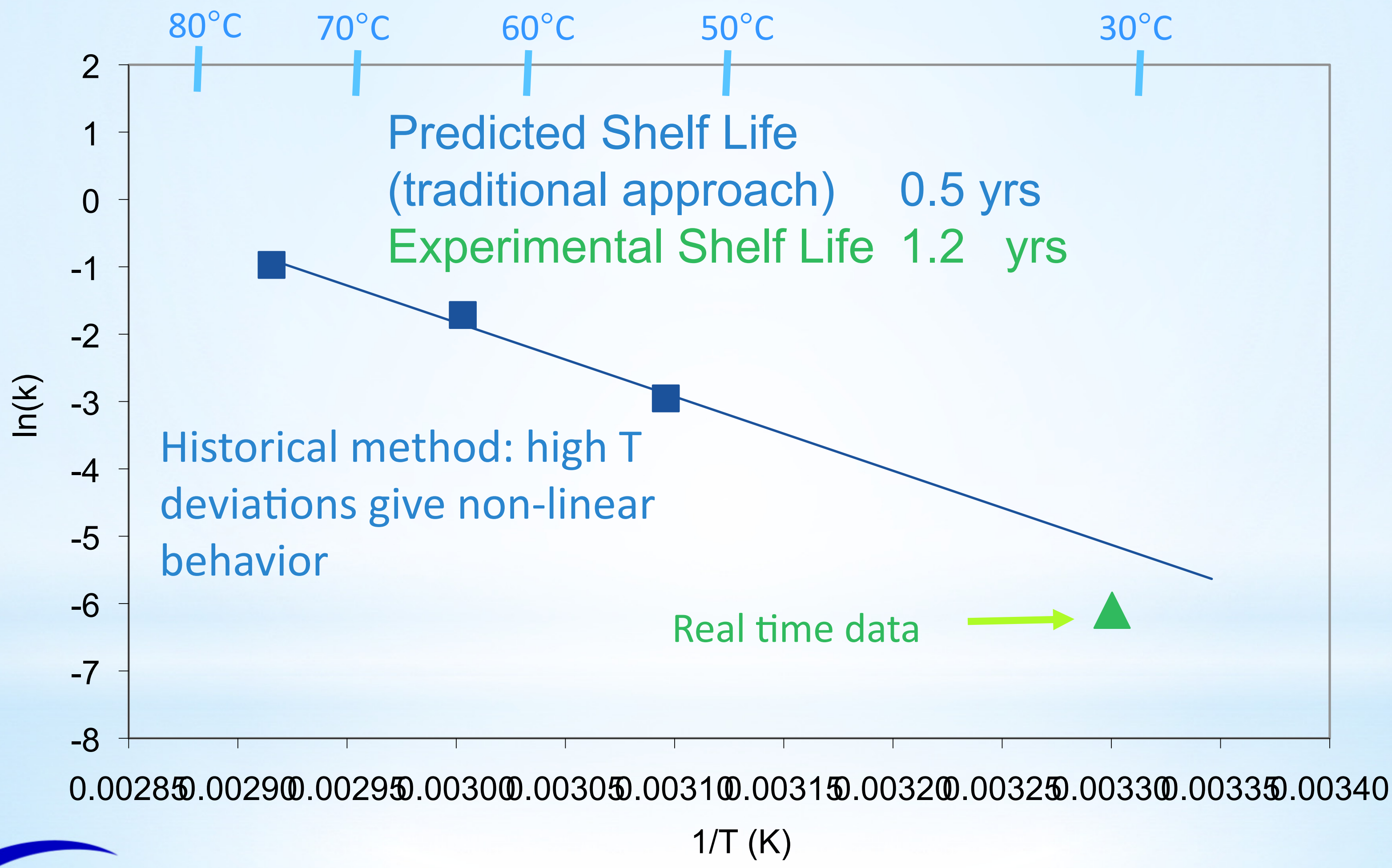


ASAP: Accelerated Stability Assessment Program (Isoconversion)



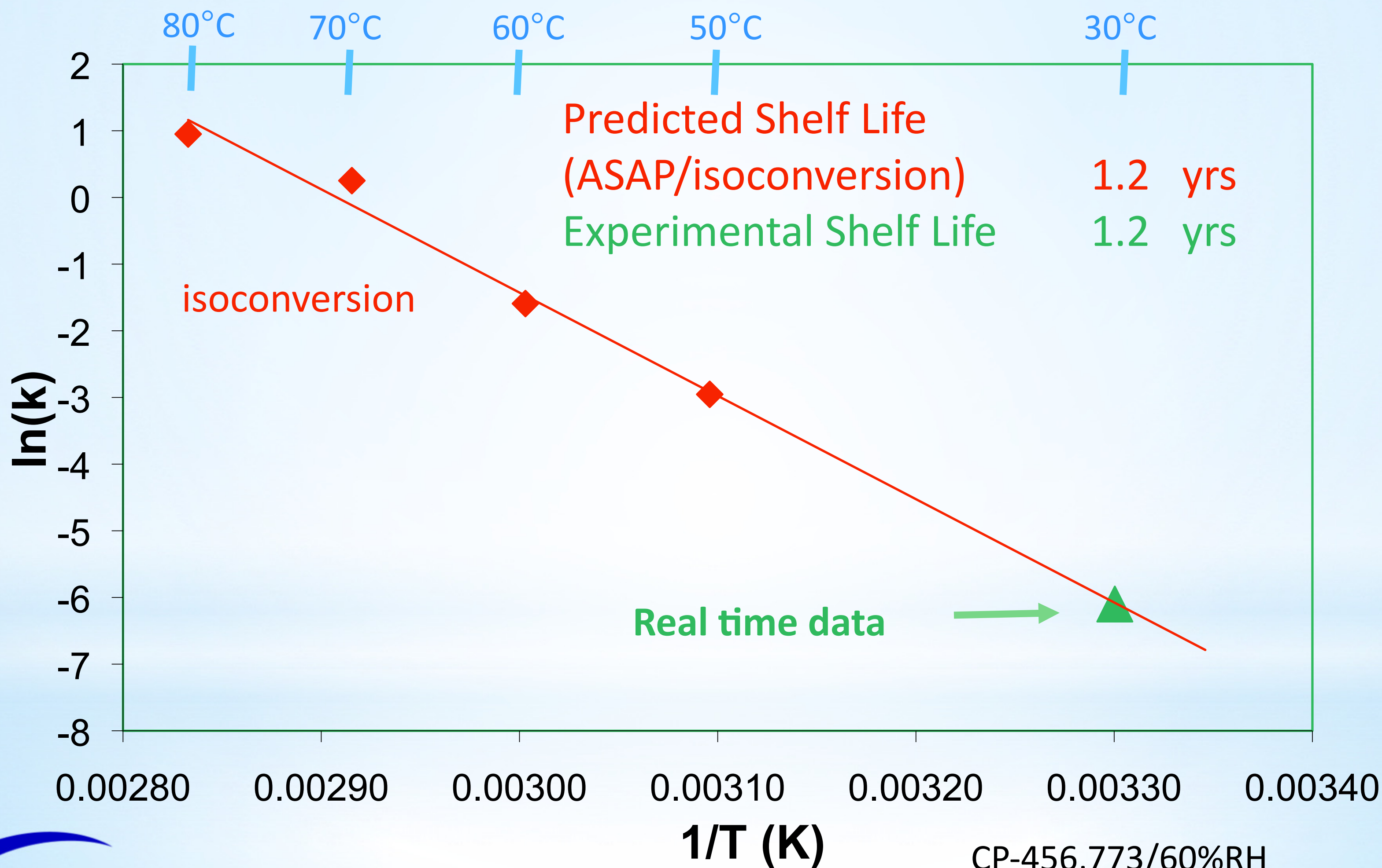
ASAP approach: % degradant fixed at specification limit, time adjusted as needed

Accelerated Stability: Traditional Arrhenius Approach



CP-456,773/60%RH

Accelerated Stability: ASAP Approach



CP-456,773/60%RH

Impact of Activation Energy on Accelerated Stability Studies

Weeks accelerated equivalent to 2 yrs at 30°C			
E_a (kcal/mol)	40°C	60°C	80°C
12 **Low activation energy**	58	24	14
29 **Average activation energy**	18	1	0.3
39 **High activation energy**	6.5	0.1	0.01

Accelerated Aging: Small Molecule Solids (Lyophiles)

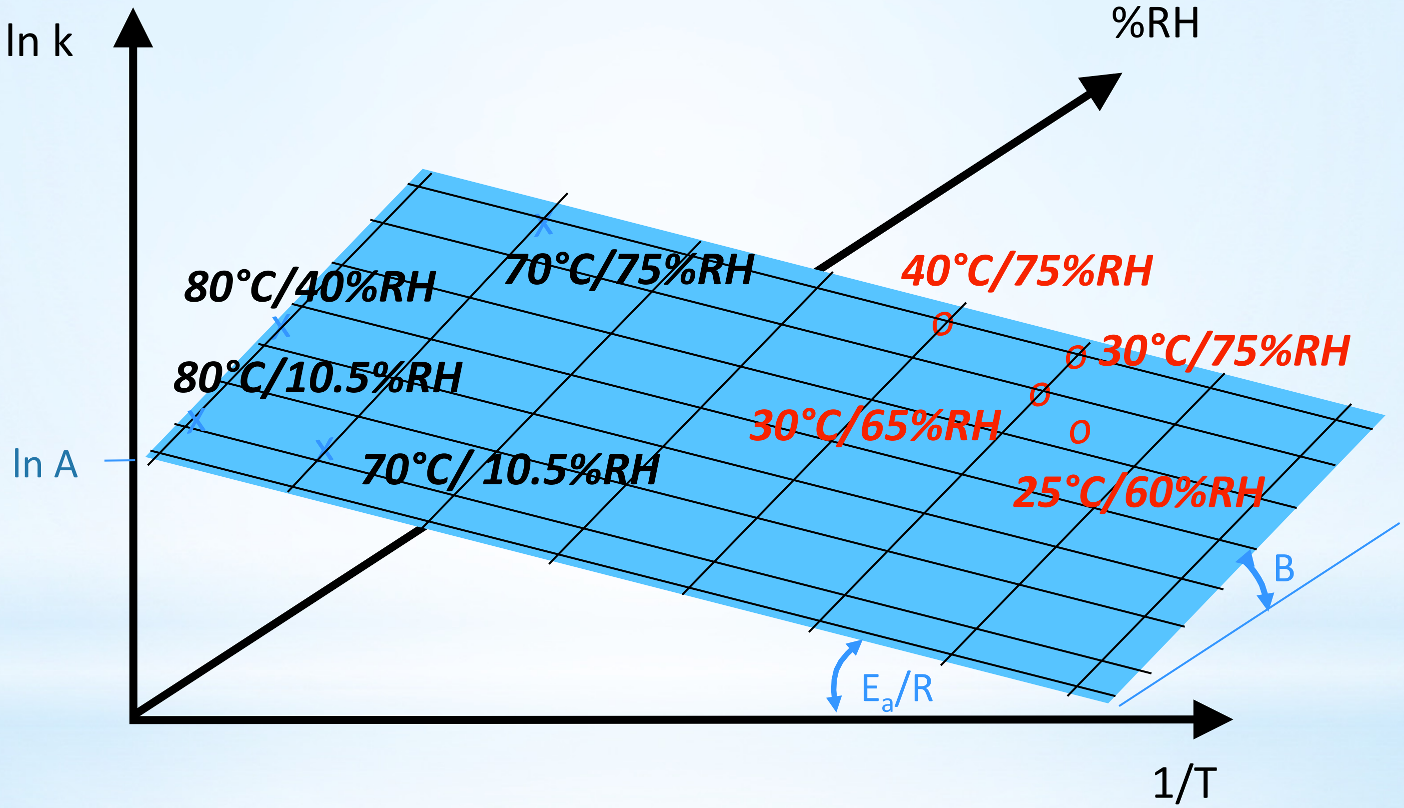
Humidity Corrected Arrhenius Equation

humidity sensitivity factor

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

Typically lyophiles are at <15% RH: equation still applies

Accelerated Stability Assessment Program (ASAP)

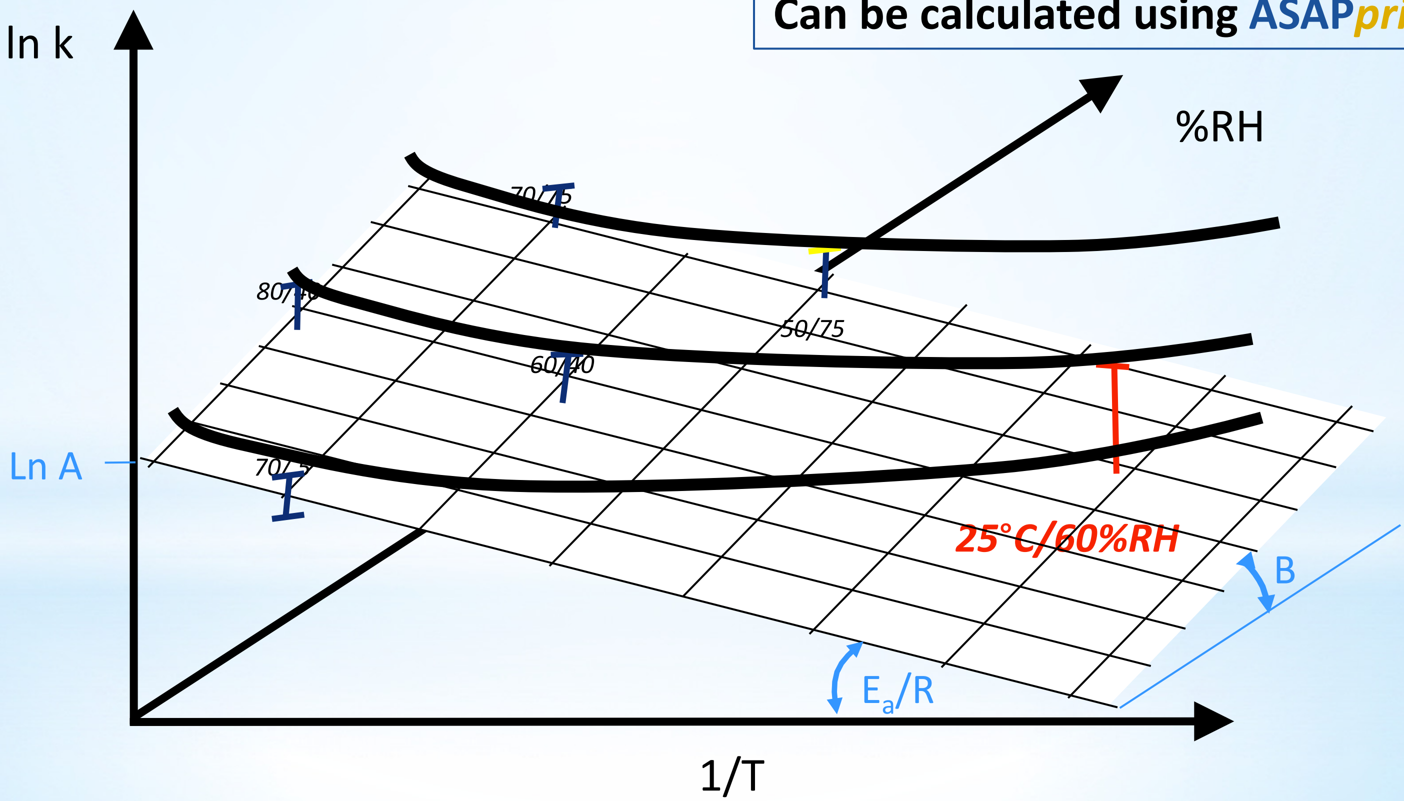


Note: RH dependence does not imply hydrolyses

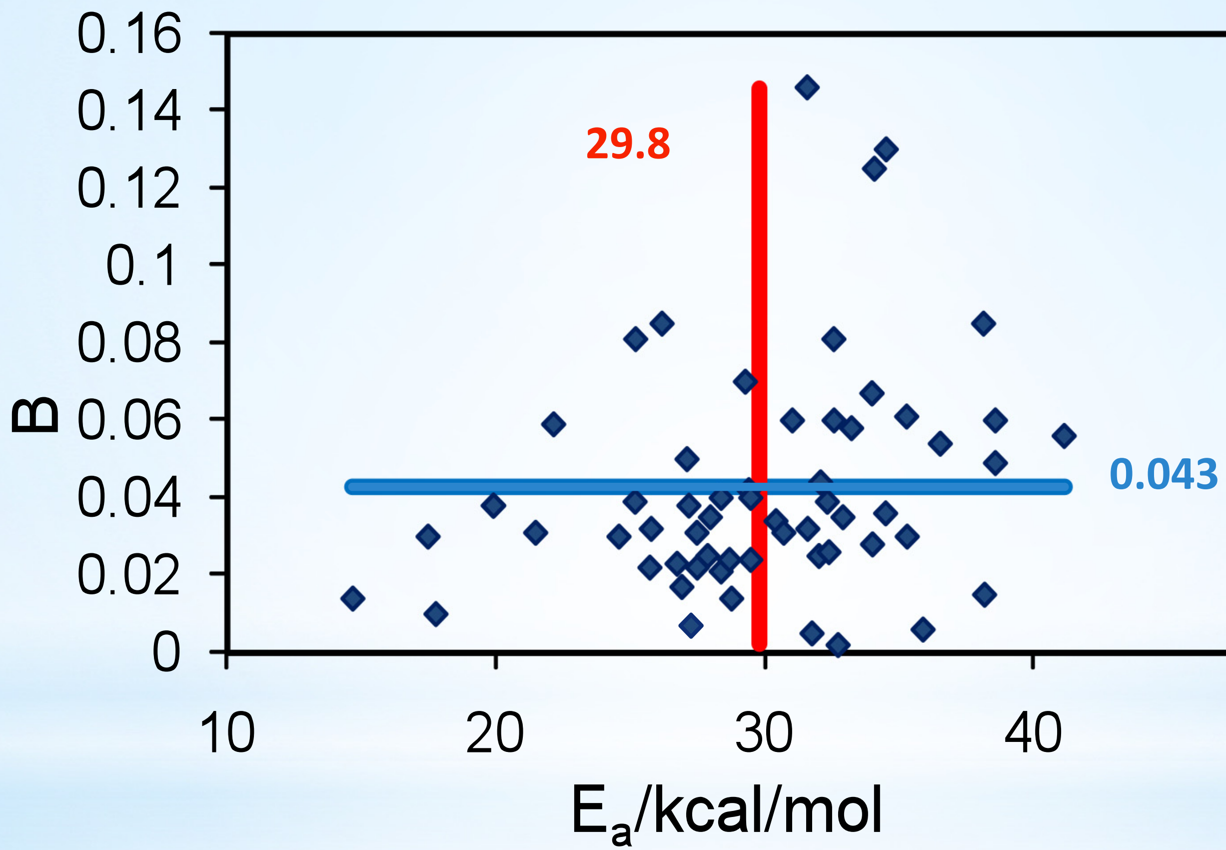
Error Bars in Accelerated Aging

Example: Confidence Interval
For 2 year shelf life (25°C/60%RH) = 95%
For 3 year shelf life (25°C/60%RH) = 75%

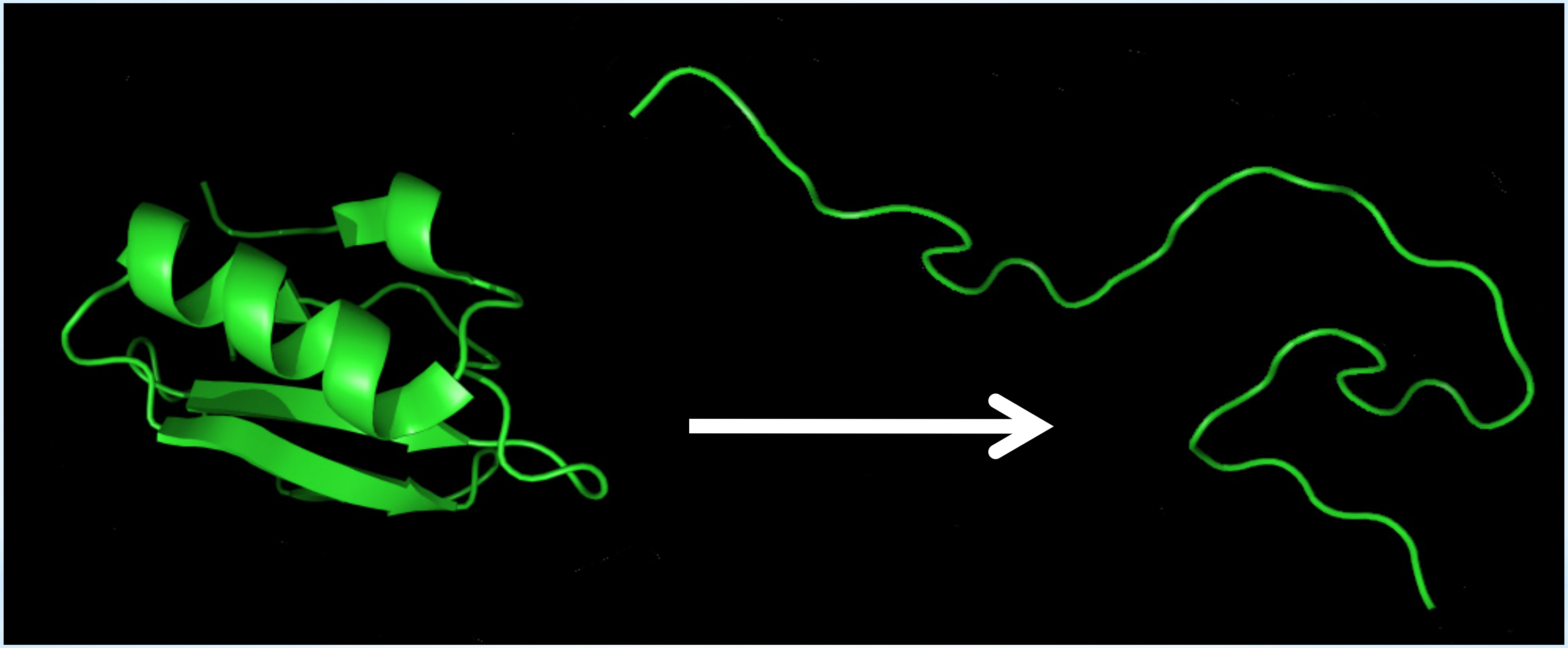
Can be calculated using ASAP*prime*™



Typical E_a and B values (n=60)



Protein Unfolding



Folded "native" protein:
Active Form

Unfolded protein:
Inactive Form

Protein Denaturation

4°-Structure

- Subunits dissociated
- Subunits disrupted

3°-Structure

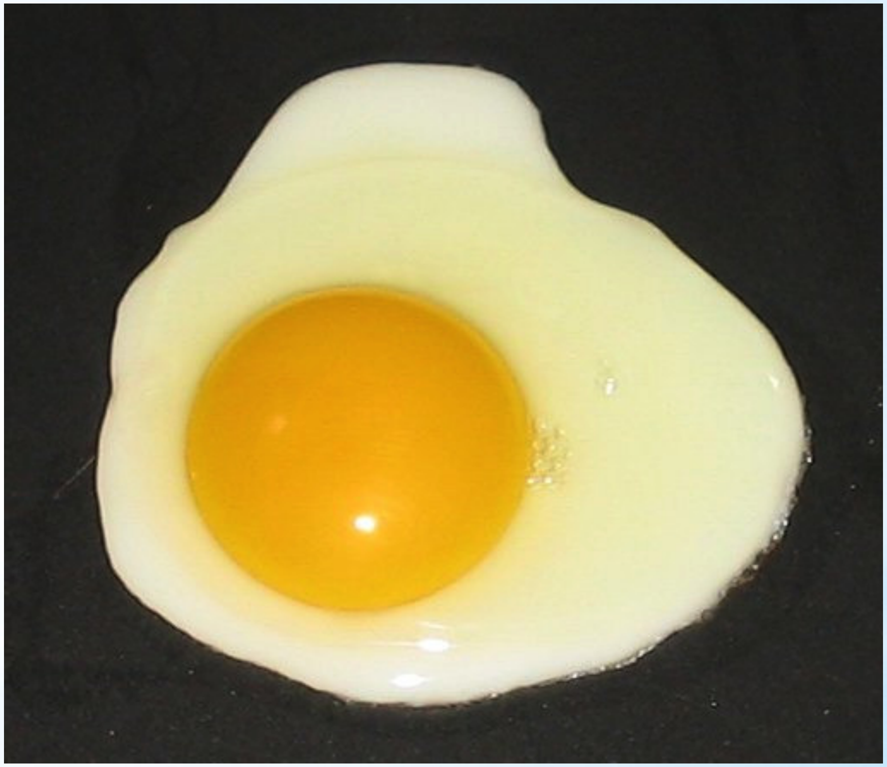
- Covalent interactions disrupted between amino acid side chains
- Dipole-dipole interactions between amino acid side-chains with themselves and solvent disrupted
- Van der Waals interactions disrupted between nonpolar amino acid side-chains

2°-Structure

- loss of repeat patterns (α-helices, β-sheets)

1°-Structure

- Not impacted



Protein Inactivation

$$N \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} U \xrightarrow{k_2} D$$

N = native

U = unfolded

D = denatured

$K = k_1/k_{-1} = \exp(-\Delta G/RT)$

$K = 1$ when $T = T_m$

Packaging

- **Solids**
  - Mostly concerned with moisture protection; RH as a function of time
  - Can be predicted accurately (**ASAP*prime*™**)

- **Solutions**
  - Packaging (container, closures) more integral to stability
  - Concerned with materials leaching from packaging
  - Concerned with loss of stabilizers into packaging
  - Packaging can bring catalysts into solution (even glass)

Conclusions

- Stability is a major part of drug product development
- Small molecule and large molecule drugs have different factors affecting their stability
- Accelerated stability is well-developed with small molecules, but remains challenging with large molecules
- Packaging must be considered in all stability assessments