Packaging for Stability

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Outline

- Scope
- Understanding how humidity impacts drug product stability
- Packaging
- Setting water content specifications
- Conclusions

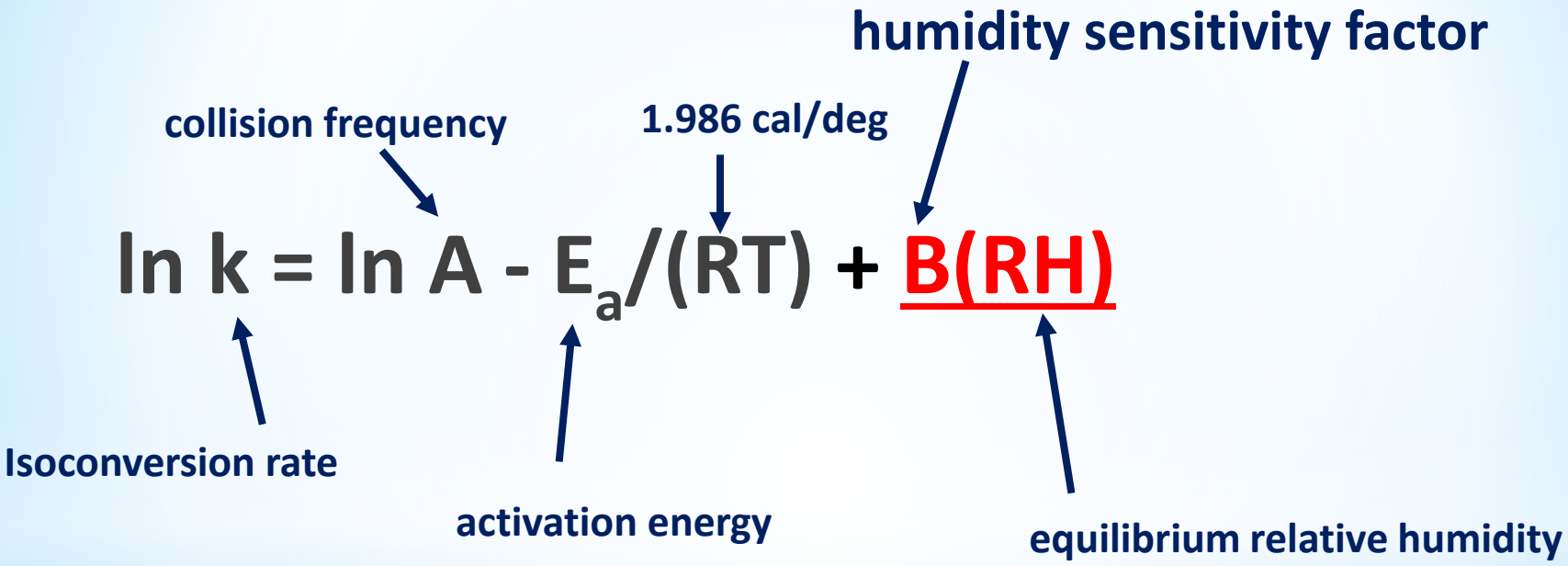
How Humidity Impacts Drug Product Stability

- Humidity sensitivity common for most degradation mechanisms:

  Humidity sensitivity does not implicate hydrolyses!

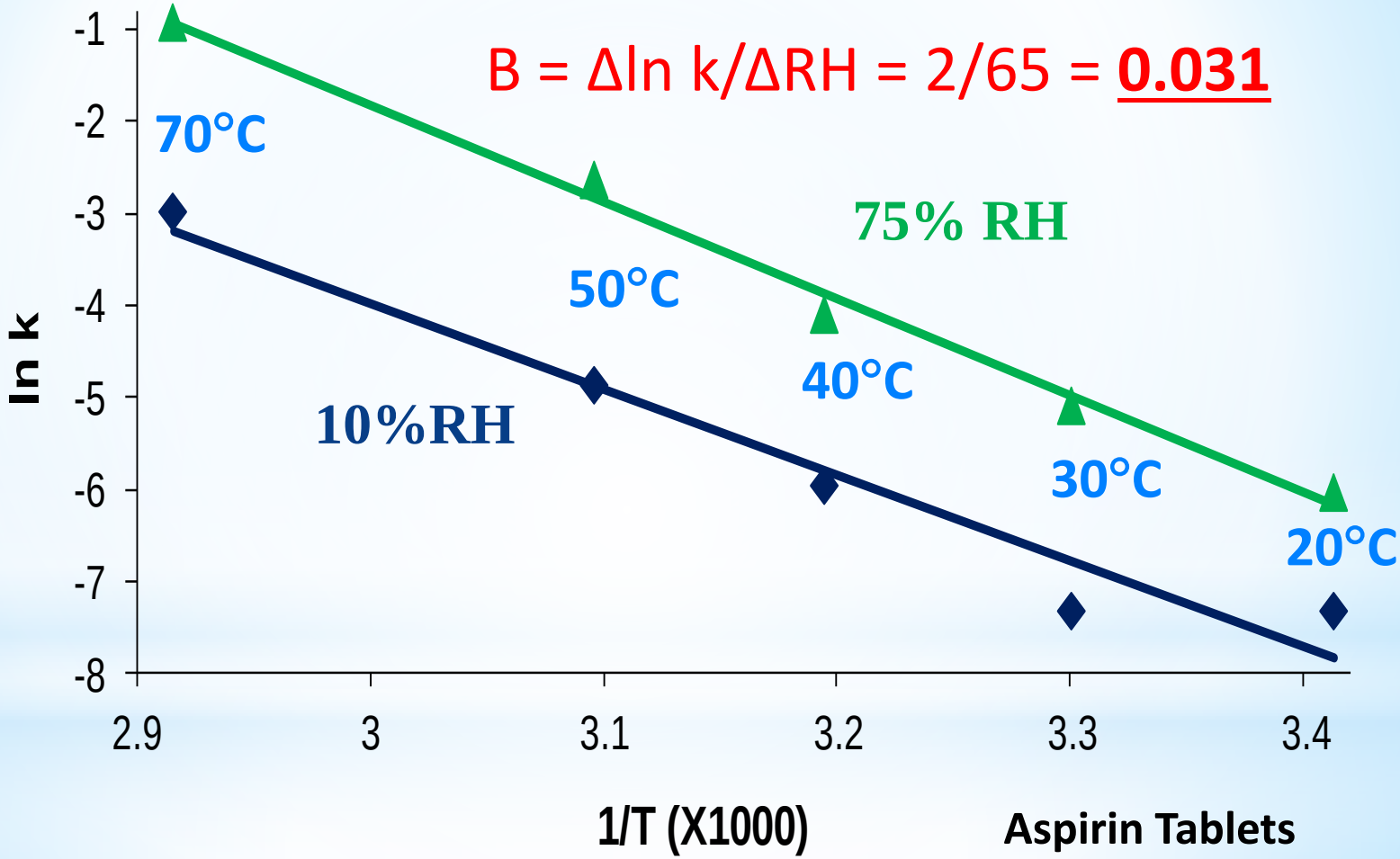
- Humidity impacts mobility

Humidity Corrected Arrhenius Equation

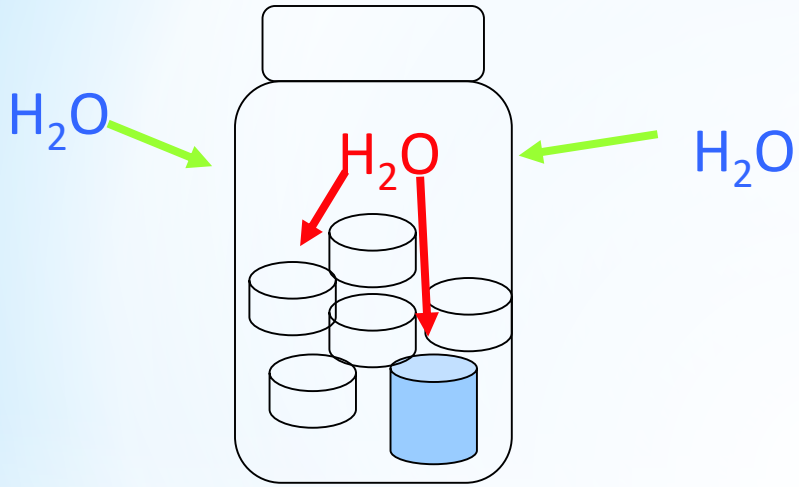


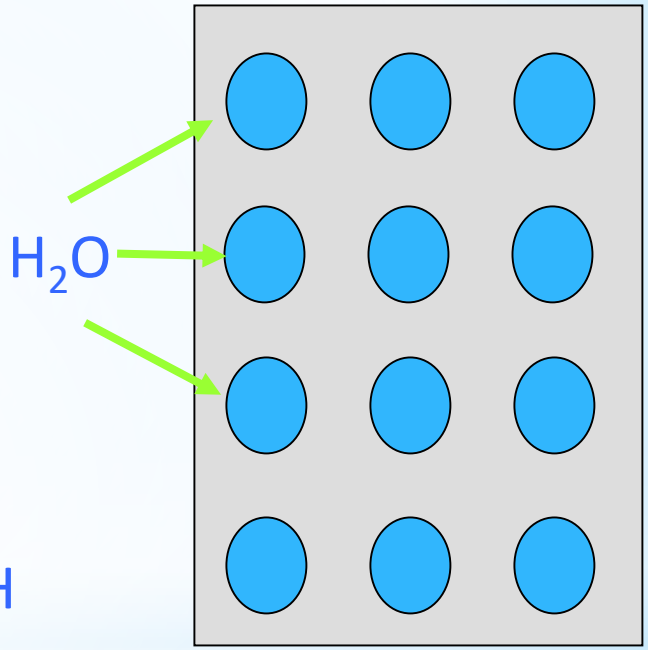
Equation universally true!
(exception: phase transitions)

Example of Humidity Impact on Drug Product Stability



Packaging for Moisture Protection

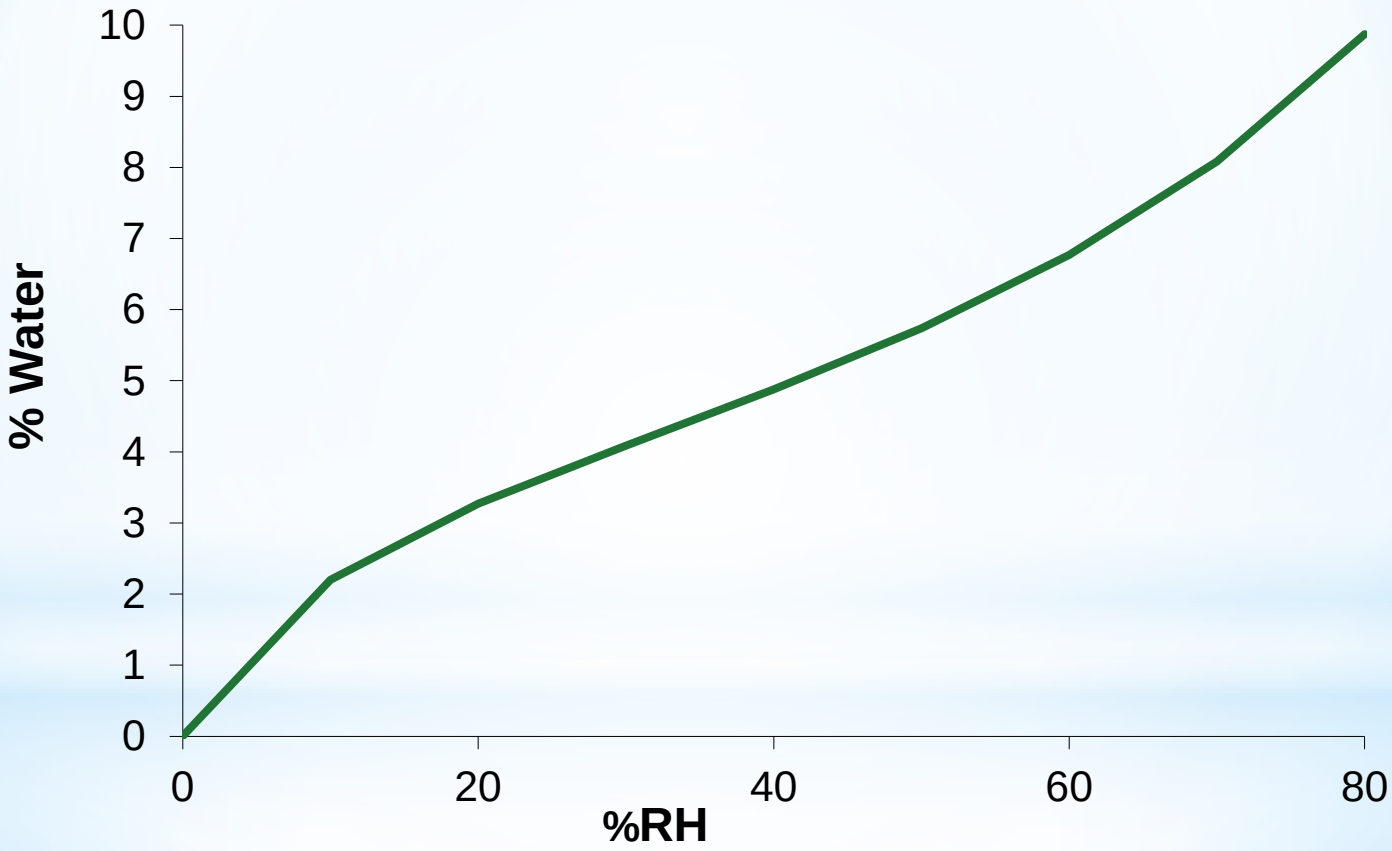




Moisture transfer depends on **MVTR** + ΔRH

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

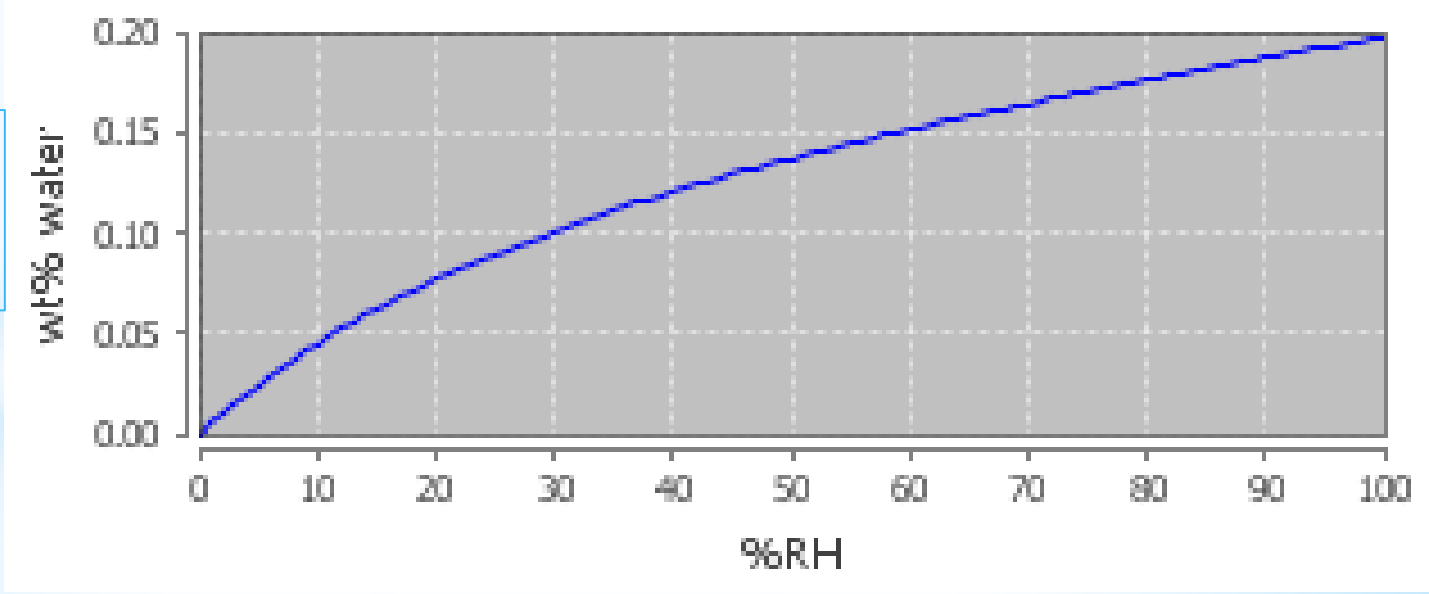
Moisture Sorption Isotherm—
Microcrystalline Cellulose



Moisture Sorption of API

- Most crystalline APIs do not adsorb much water
- Program uses an “average” API based on 35 literature APIs
- Some APIs may differ significantly from the assumed sorption isotherm

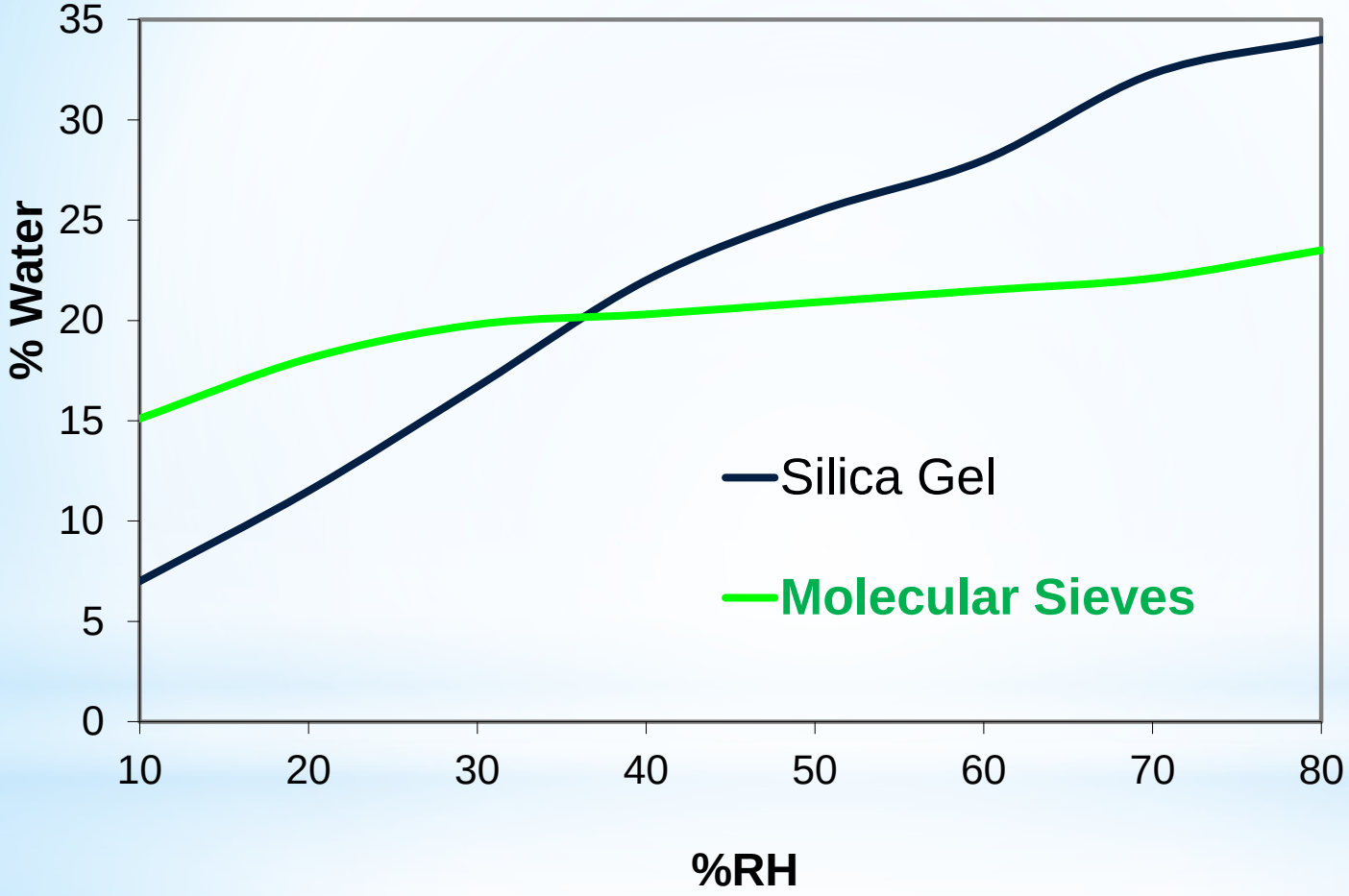
Note scale!



Drug Products

- Sorption isotherm of solids do not affect each other
  - Isotherm for mixture = weighted average of components at each RH

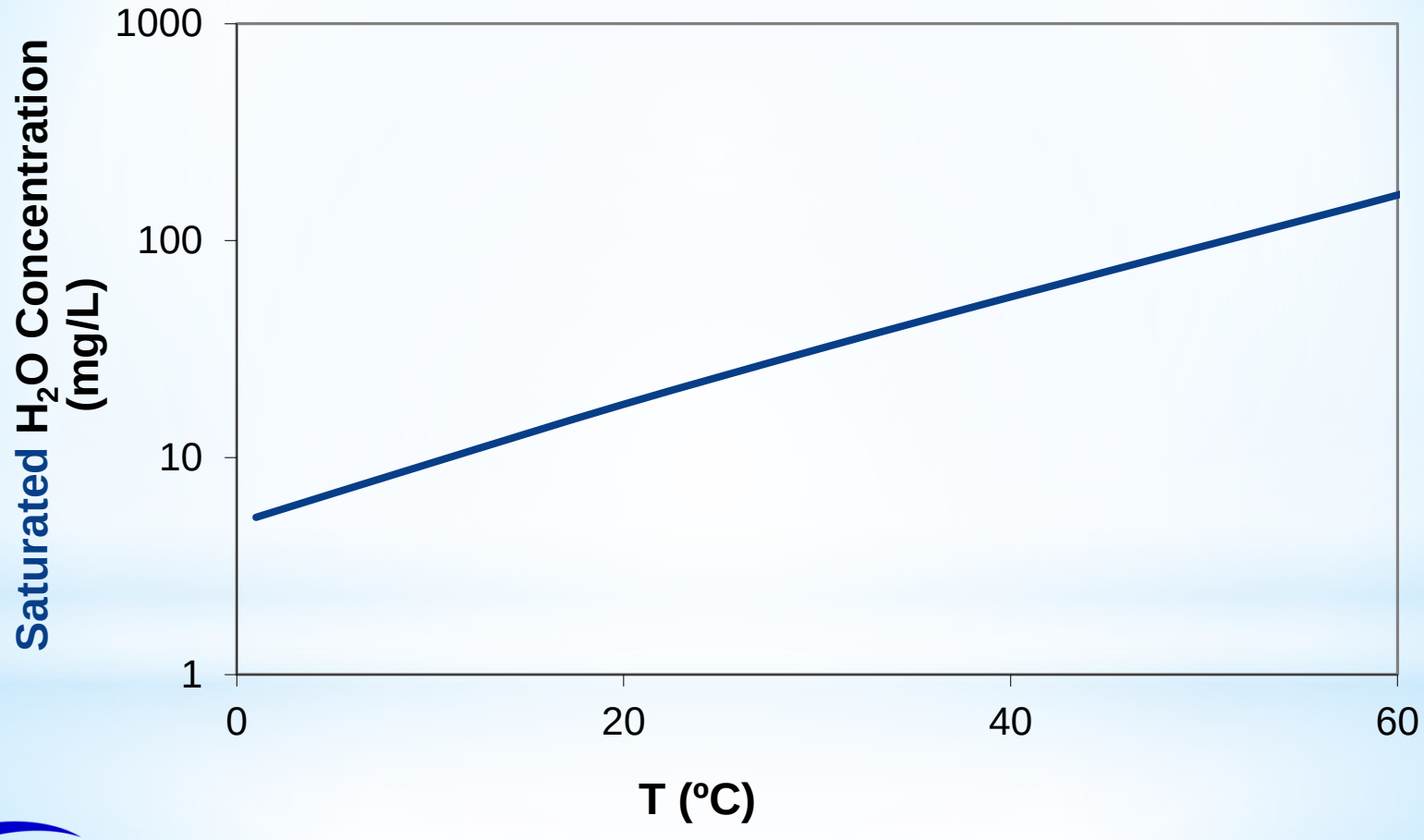
Moisture Sorption Isotherm—Desiccants



Molecular sieves have a fixed capacity

Silica gel sorption depends on RH

Head Space Moisture



Moisture Accounting Example

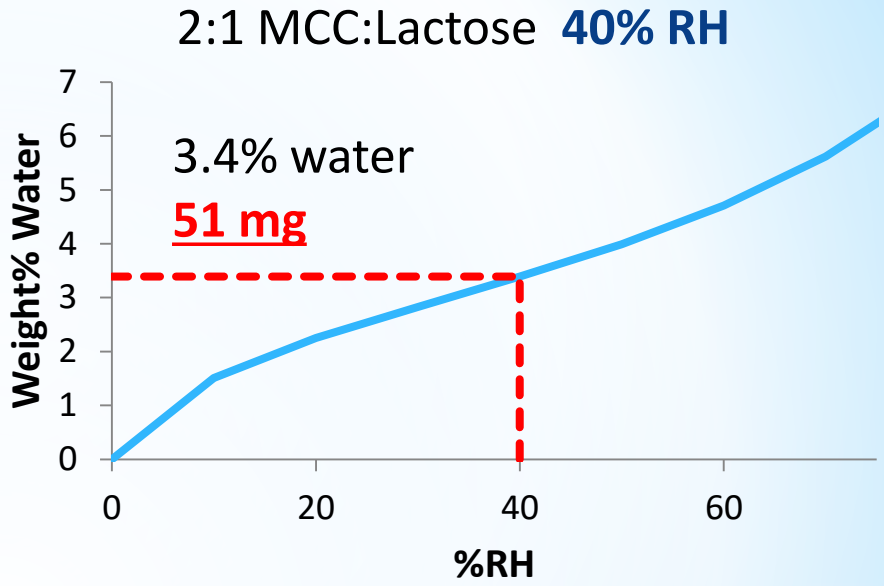
30 X 500-mg tablets

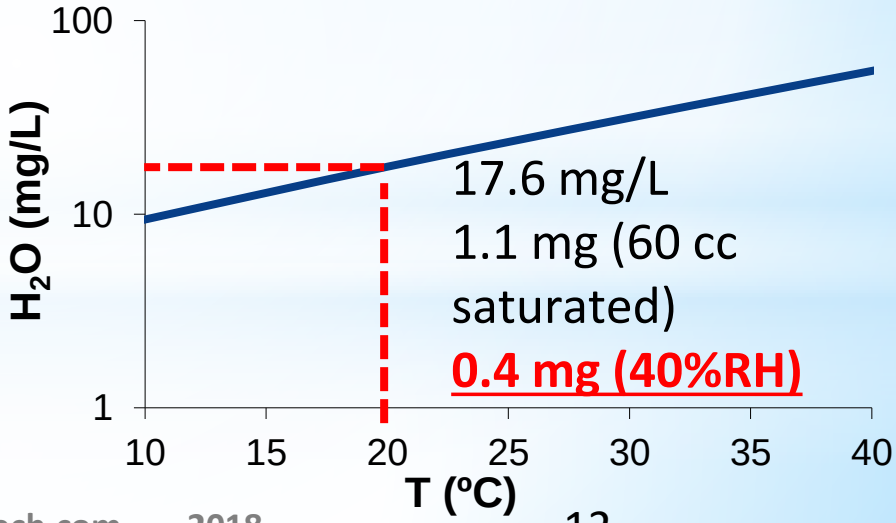
20°C/60-cc bottle

0.4 mg H_2O headspace/

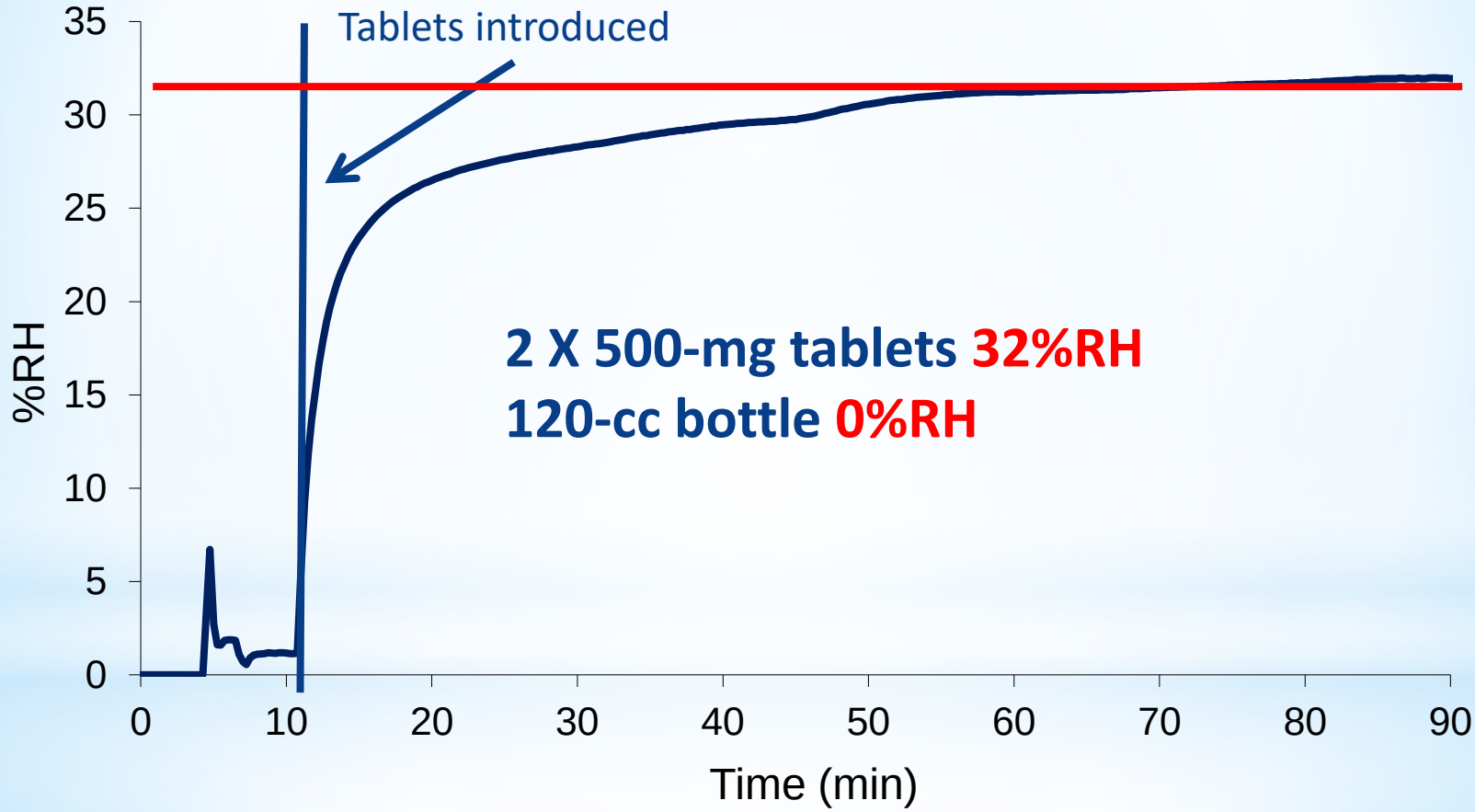
51 mg H_2O in tablets

Headspace H_2O not very significant!

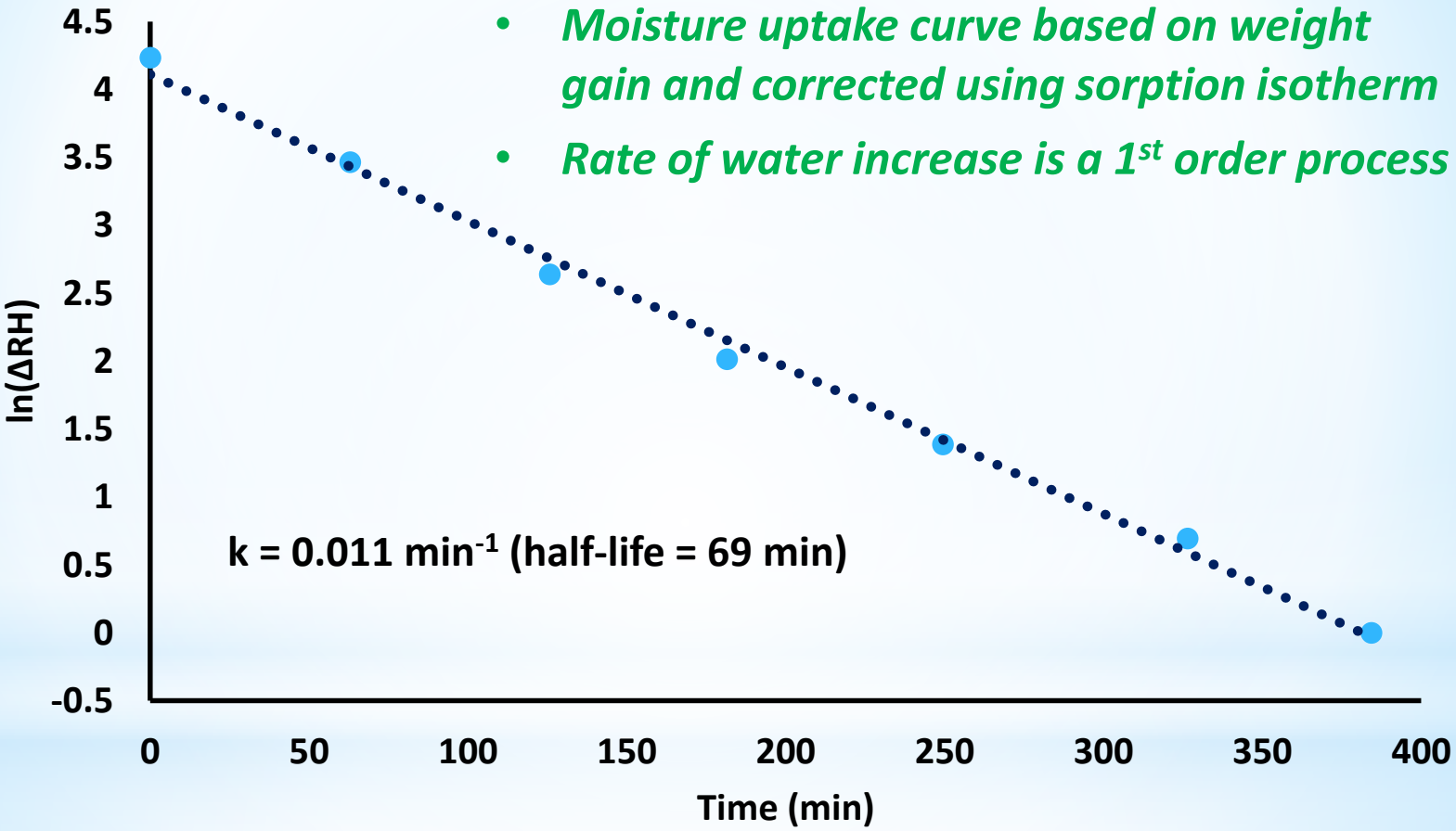




Moisture Equilibration in Packaging:
Very Rapid!



Tablet Moisture Sorption: Rate Transformation



- *Moisture uptake curve based on weight gain and corrected using sorption isotherm*
- *Rate of water increase is a 1st order process*

Moisture update into tablets can impact stability

Typical Half-lives for Moisture Equilibration

- Powders 10-20 min
- Uncoated tablets 60-90 min
- Cosmetic film-coated tablets 2-4 hrs
- Moisture protected film-coated tablets 1-2 days

Note: Protective coatings can be good for in-use, but do not make a difference in long-term stability

Relative Humidity as a Function of Time

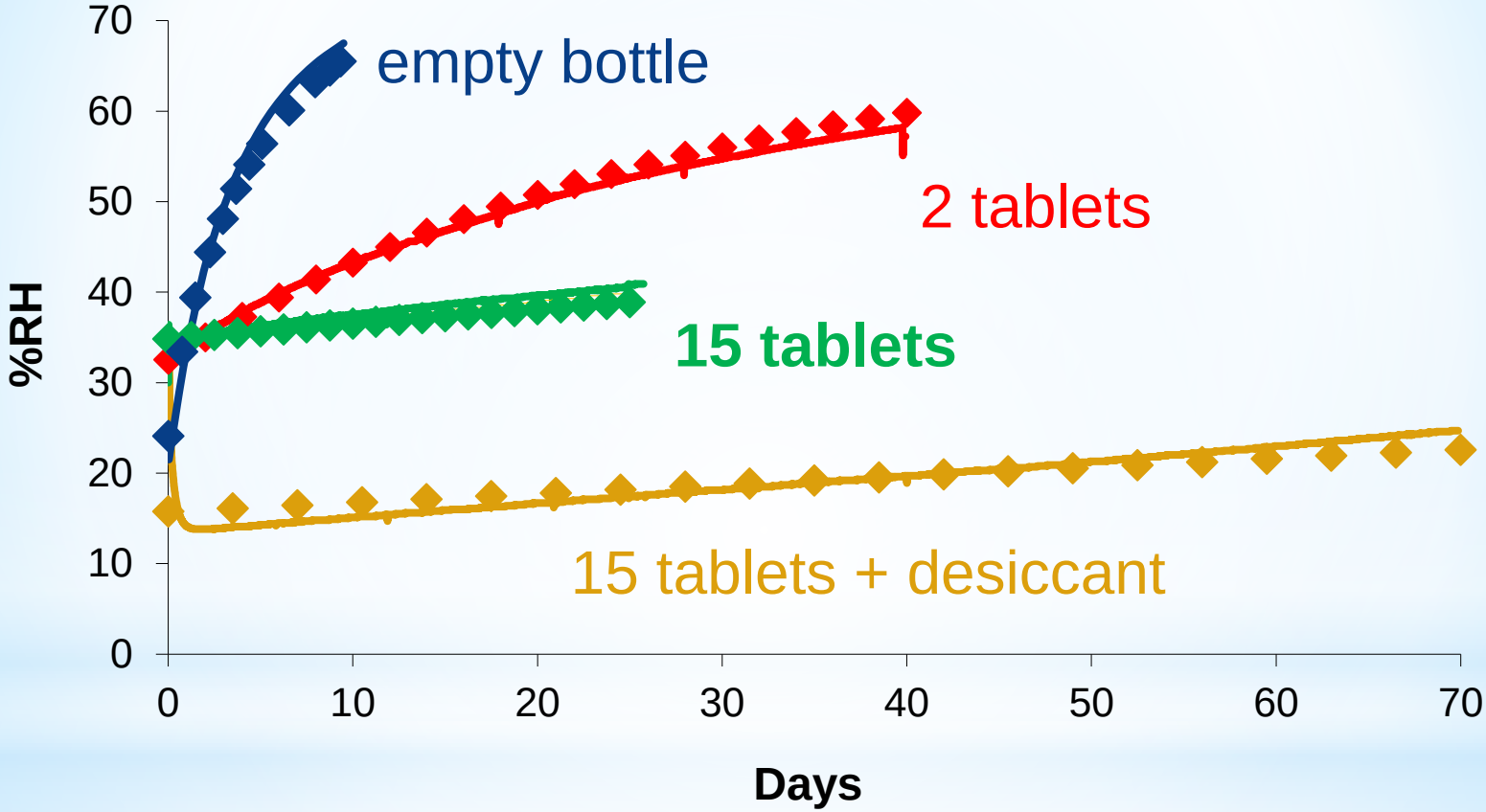
Exactly predicted from easily measured information:

1. **MVTR**
2. **moisture sorption isotherm**
3. **headspace volume**
4. **external RH, T**

MVTR Issues

- Standard methods for measuring MVTR for sealed packages
  - Gravimetrically (weight gain of desiccant in package)
    - **USP24/NF36 (Ch. 671) 40°C/75%RH**
    - ASTM 3079 37.8°C [100°F]/90%RH
- Assumes MVTR is independent of temperature, but it really does depend heavily on temperature
- Ignores that MVTR depends on RH
- Often done on sheets without accounting for blister or bottle-forming process (units often per area not per package)

Predicted (Lines) vs. Measured RH

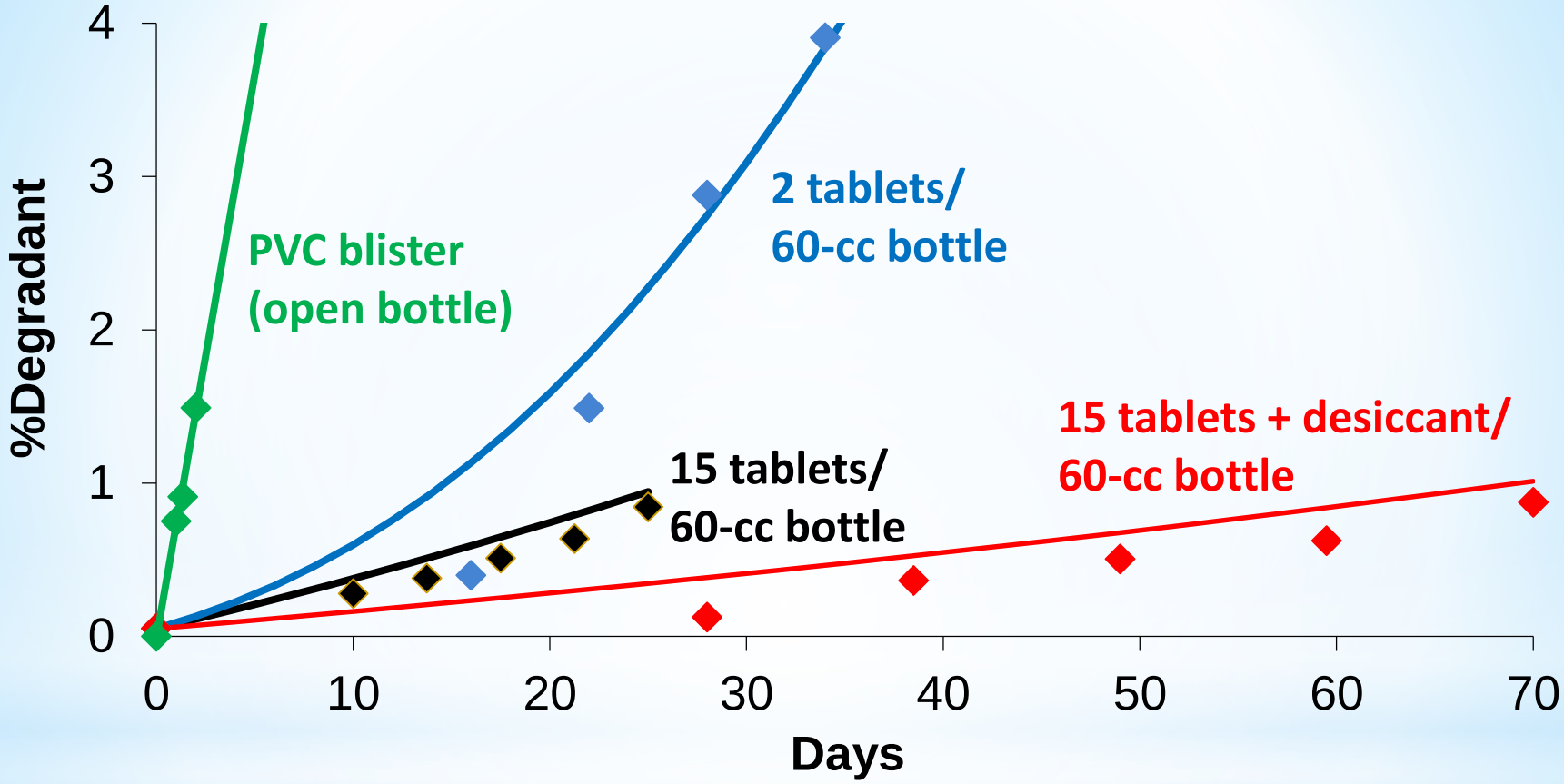


500 mg tablets 60-cc HDPE Bottles (40°C/75%RH)

Combining Moisture Sensitivity with Packaging Protection

- Can use ASAP*prime*® to determine RH/T sensitivity of drug product
- Can explicitly determine RH as a function of time for any packaging + storage conditions
- Can combine to determine shelf-life of drug products under any packaging + storage conditions

Example



Lines: predicted (**ASAP*prime*®**)

Diamonds: experimental

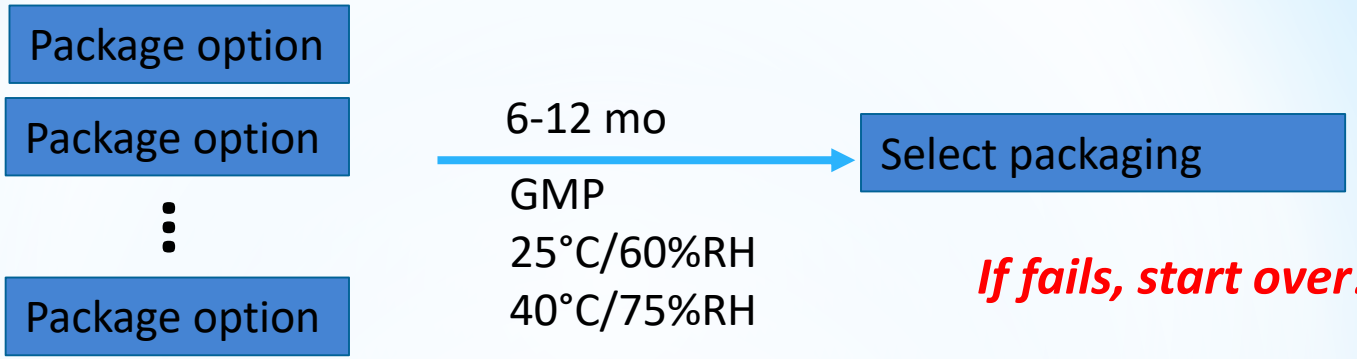
CP-481,715 in 60-cc HDPE Bottles (40°C/75%RH)

B = 0.068

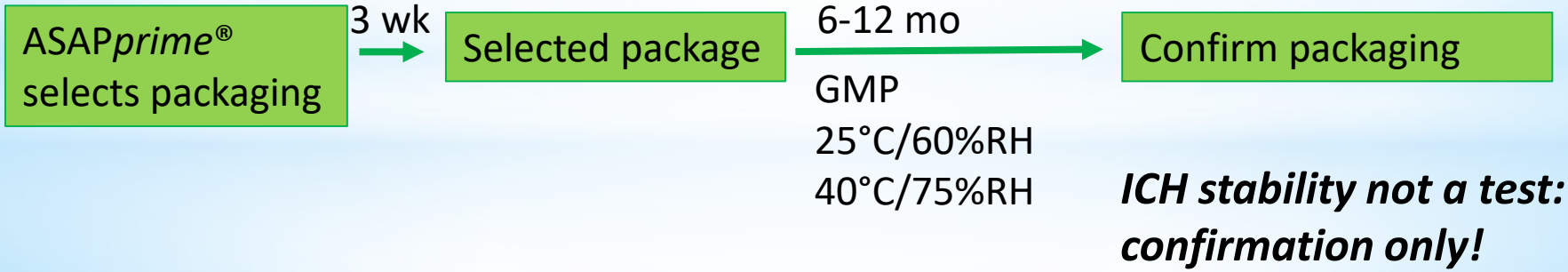
Using ASAP*prime*® for Packaging

Traditional Packaging Screening

3-8 packaging options



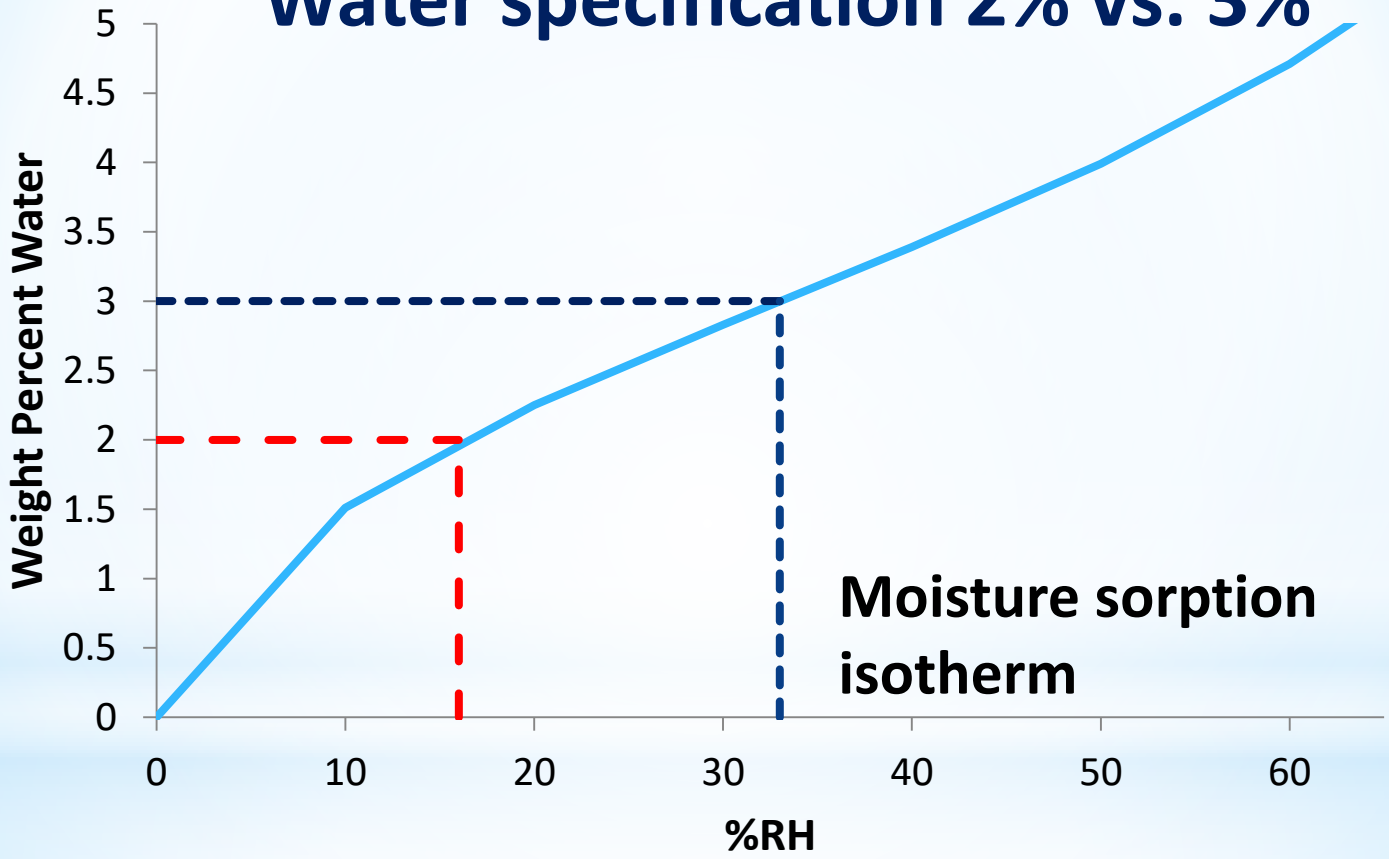
ASAP-Based Packaging Determination



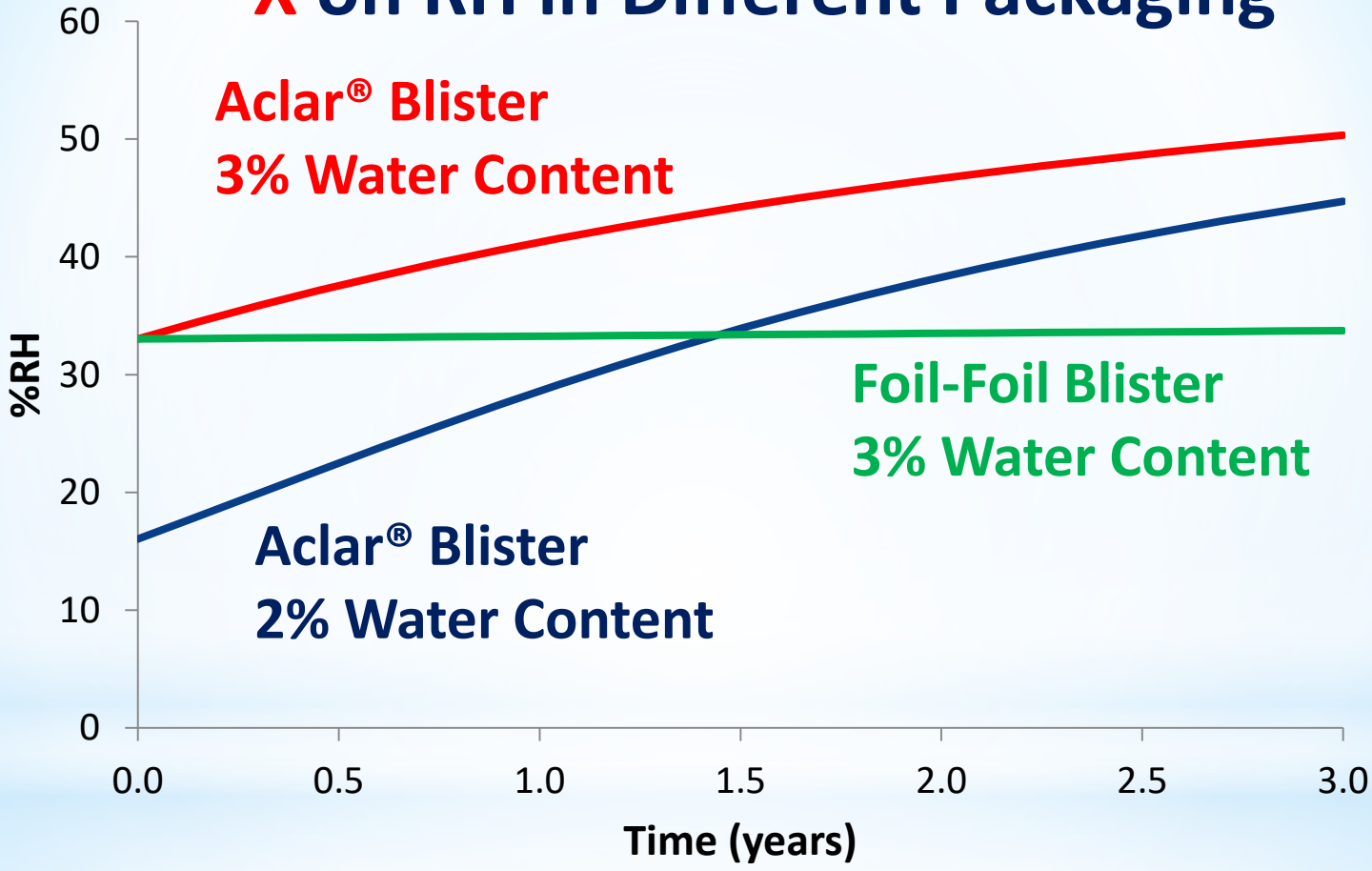
Water Content Specifications

- Water content at packaging impacts drug stability in most cases
- Specifications can be linked to RH impact + packaging

Example:
Drug Product X
Water specification 2% vs. 3%

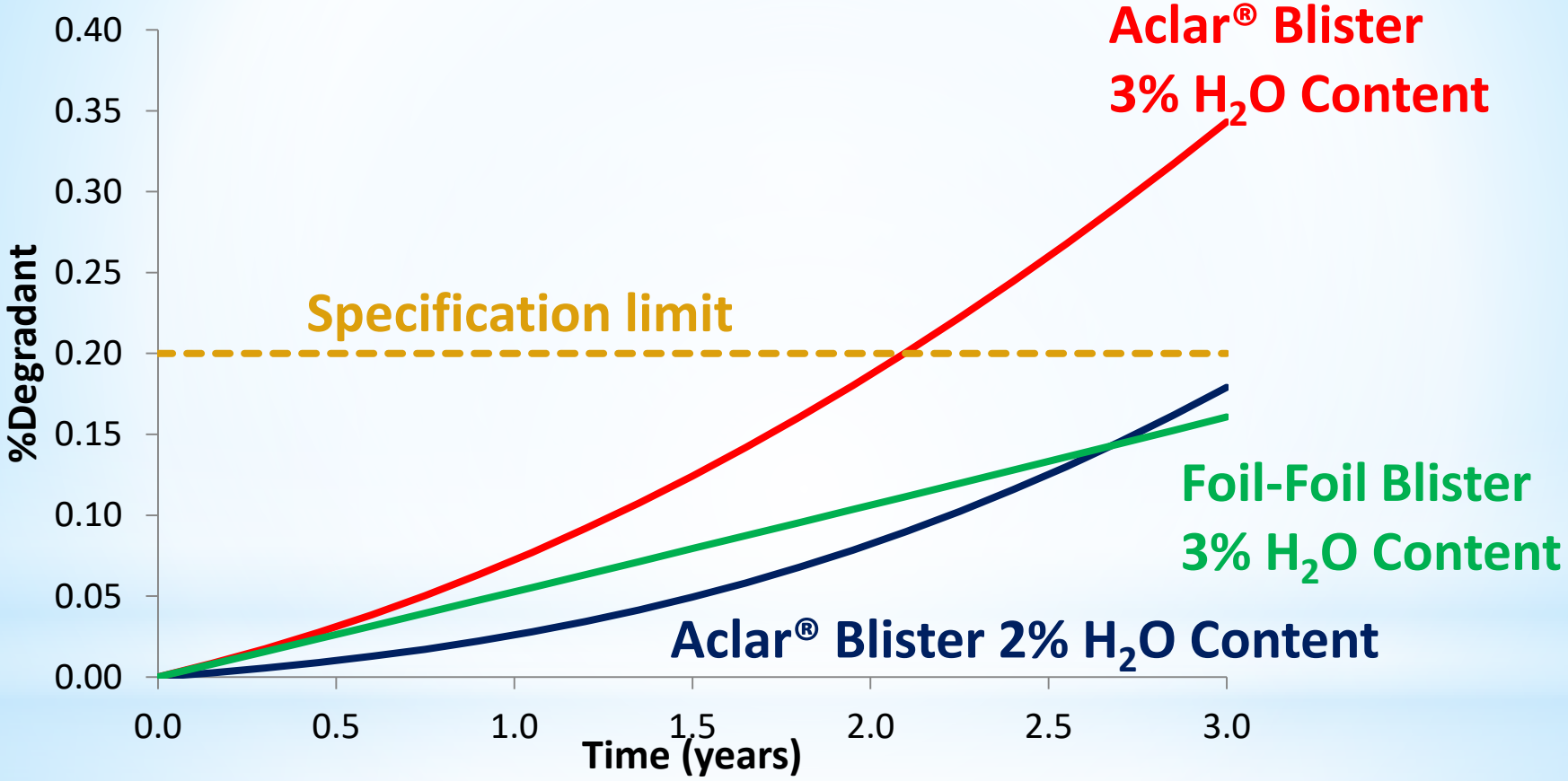


Impact of Initial Water Content of X on RH in Different Packaging



25°C/60%RH

Impact of Water Specifications for X Linked to Packaging



25°C/60%RH; B = 0.07

Impact of Water Specifications Linked to Packaging

- In example, packaged in Aclar® blister get 3-year shelf-life with 2% water content limit
- With 3% water content limit, only get 2 years in Aclar®
- Can use 3% water content limit if package in foil-foil

- Can model impact of different water content, packaging configurations, climate zones using **ASAP*prime*®**

Conclusions

- Scientific methods exist to understand drug product stability and packaging choices
  - ASAP*prime*® provides a basis for both accelerating and understanding chemical stability
  - Packaging follows predictably from the data
- ASAP enables faster, more reliable decisions
- ASAP enables a potential new way for industry to meet its regulatory commitments