In-use and Excursions: Stability Beyond ICH

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Stability Beyond ICH

- In-use Stability
- Excursions

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In-Use Stability: Challenges

- Products often removed from original packaging
  - Constituted with liquid
  - Opened multiuse packaging (e.g., bottle) then dosages removed regularly or as needed
  - Dispensed from pharmacy supply bottles to patient bottles
  - Placed in patient dispensing units
- Regulatory expectation that the in-use shelf-life be actually determined

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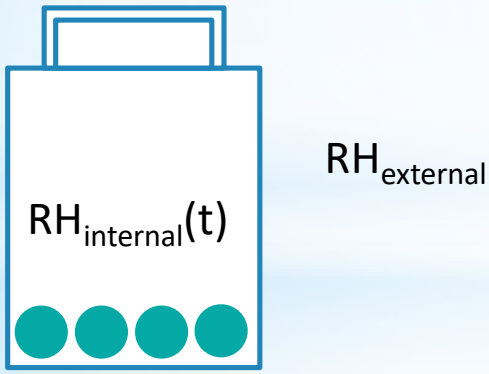
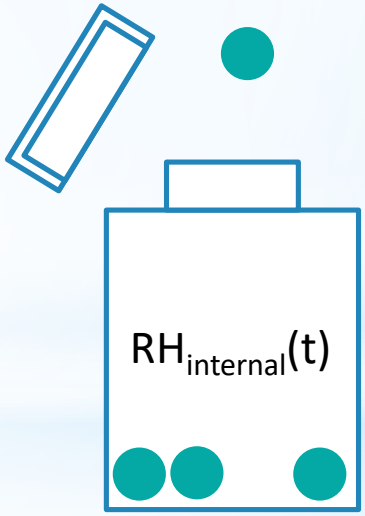
In-Use Stability: Problem Statement

ASAP*prime*® models RH as a function of time in closed containers →determines impact on shelf-life

When the container is opened periodically and some dosages removed, does the final unit dose remain within specifications?



$RH_{external}$



$RH_{external}$

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In-Use Stability: Proposed Assumptions

- Temperature, RH sensitivity for in-use equals that for the shelf-life
- Bottle open time (each dose) = 1.0 min
- MVTR of recapped HIS bottles corresponds to average MVTR for the bottle
- Dosages removed as per prescribing information; for “use as needed”, removed evenly over in-use period

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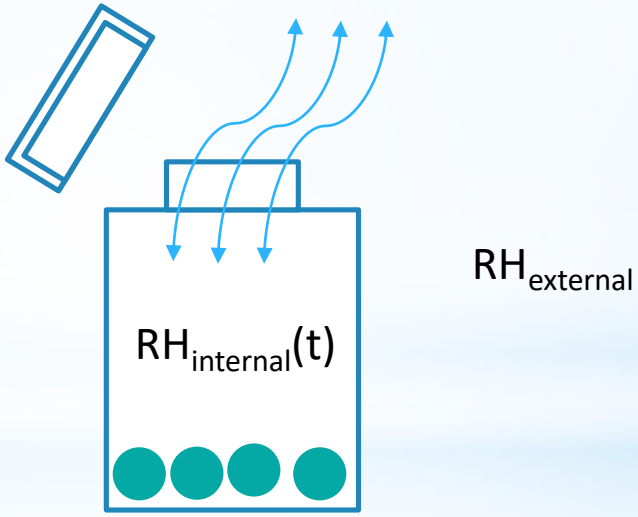
In-Use Stability

Scenario I: Open

Assume open to environment throughout use period (most conservative)

$RH_{internal}(t) = RH_{external}$

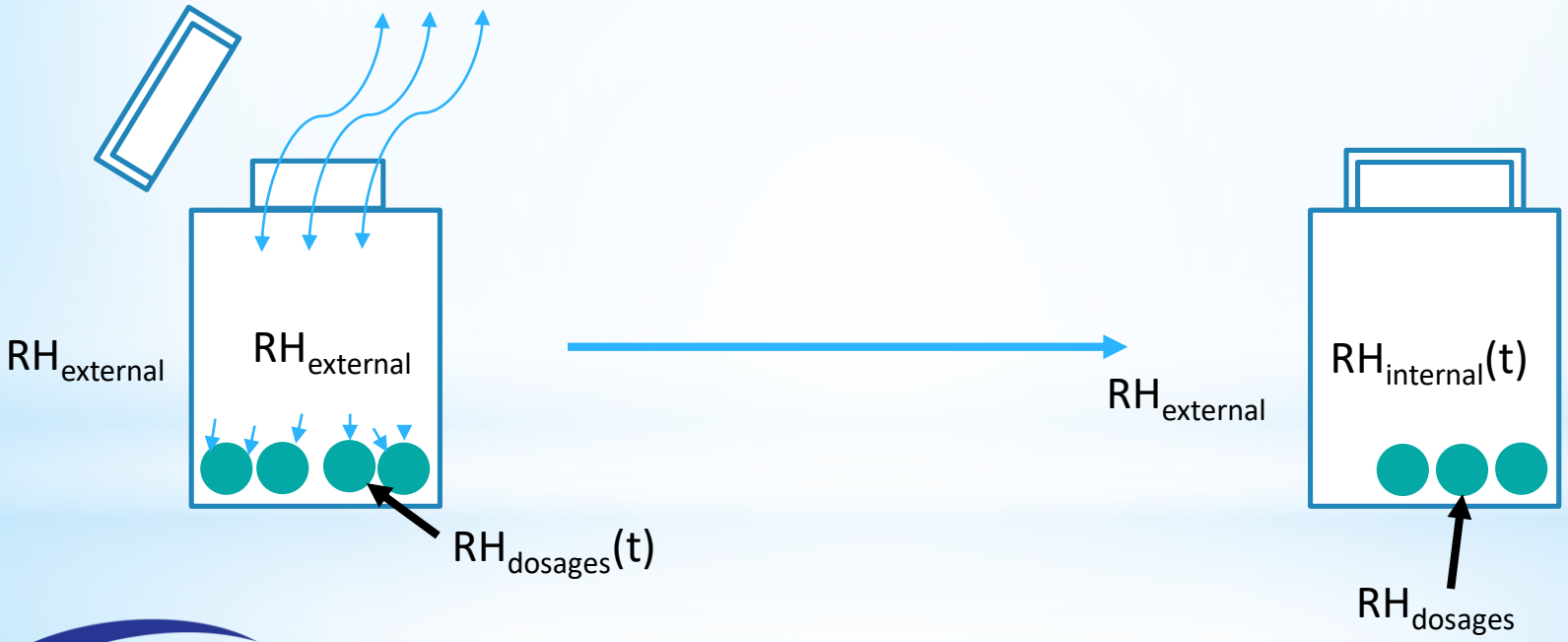


In-Use Stability

Scenario II: Headspace exchange and dosage sorption during open time

1. Headspace completely exchanged; dosages sorb H_2O

2. Bottle re-closed; recapped bottle MVTR determines RH as a function of time



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In-Use Stability: Re-capped Bottles

Two major impacts of re-capped bottles:

- Loss of foil from heat induction seal (HIS) increases bottle permeability
- Fewer dosages in the bottle over time result in more rapid change in internal RH (less buffer to moderate RH change)

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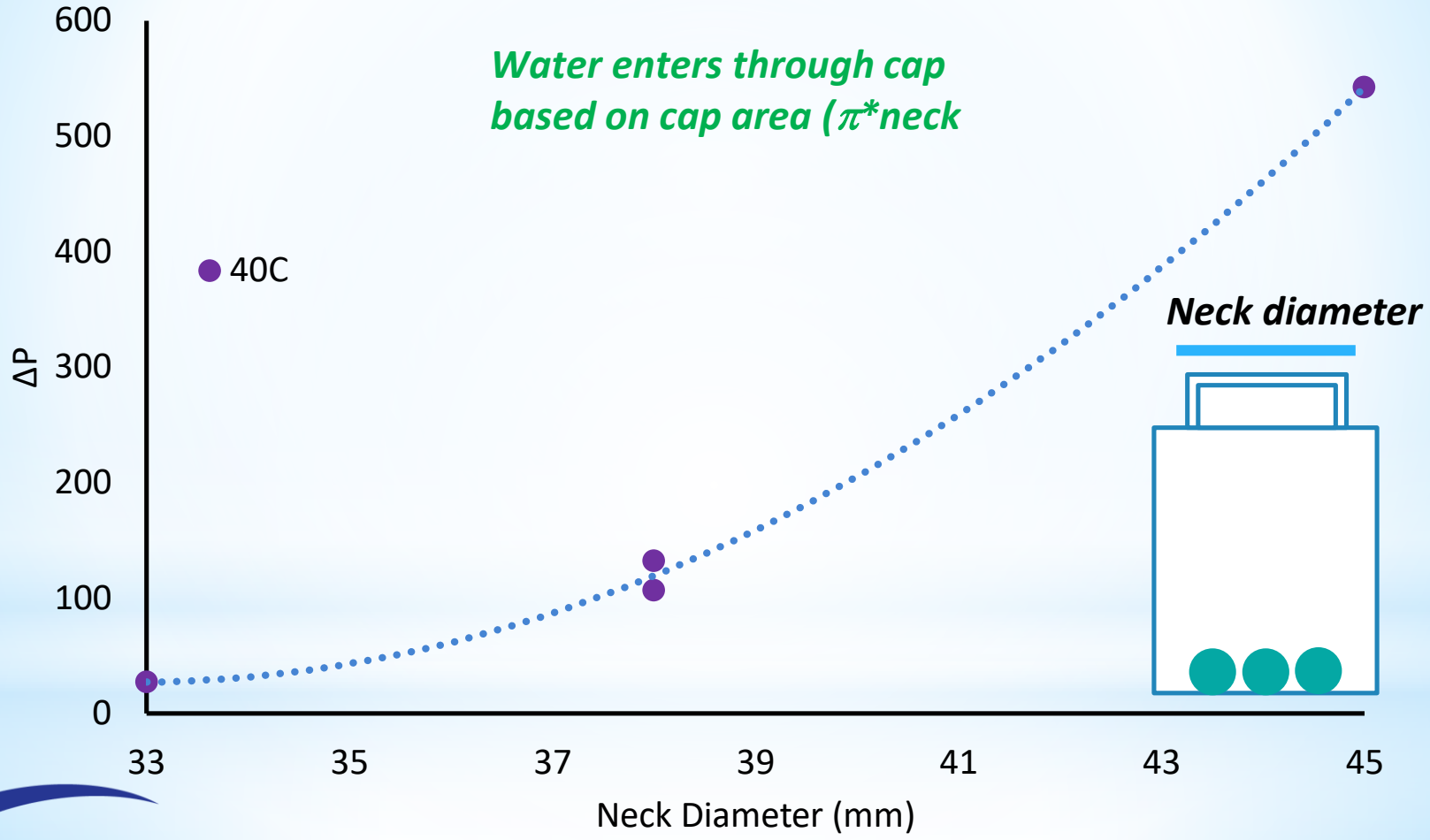
Permeability of HIS Opened/recapped Bottles (Subtracting Permeability of Sealed Bottle)



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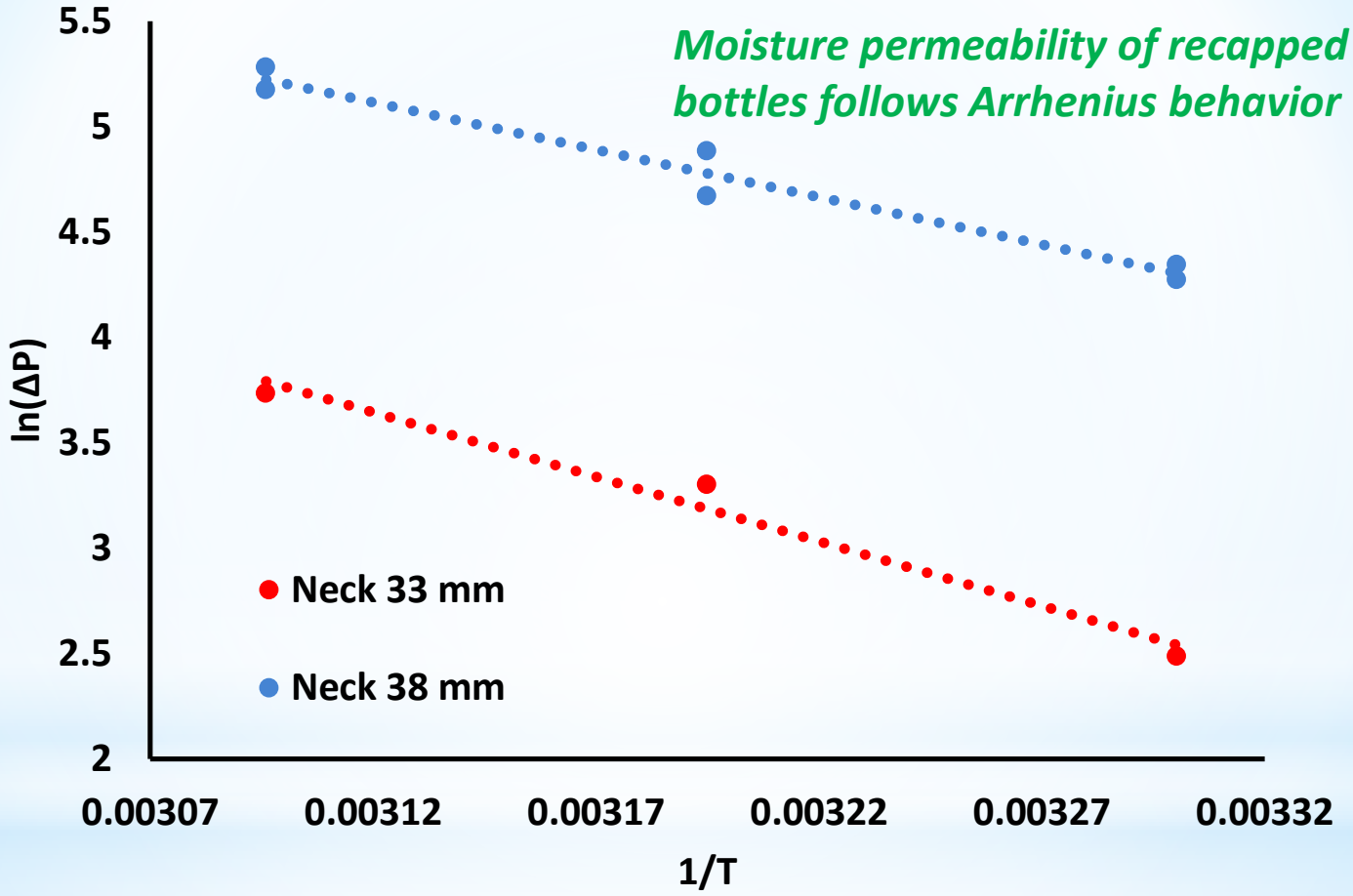
T Impact on Permeability for Recapped HIS Bottles



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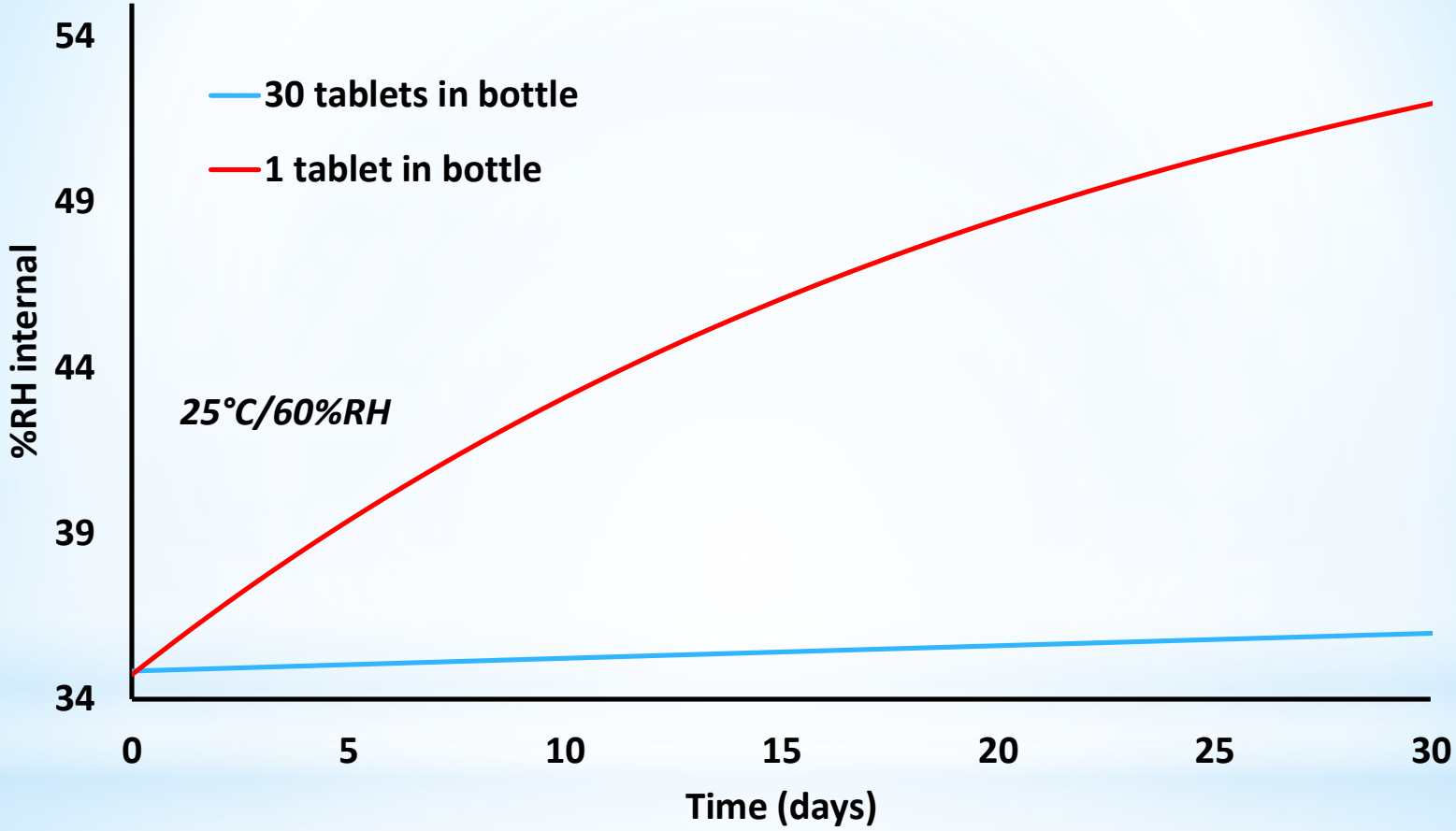
As Dosages Removed, RH Can Rise Fast Inside Bottle



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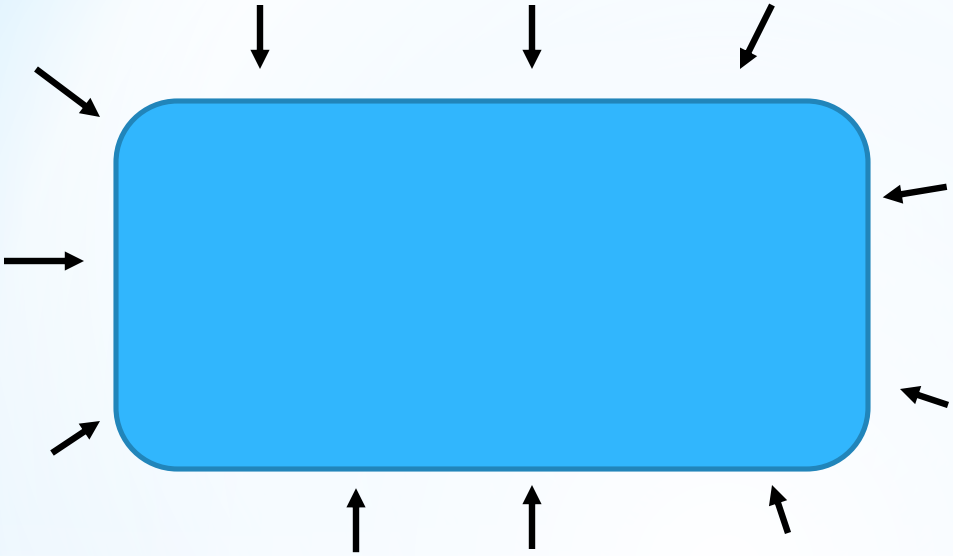
Tablet Moisture Sorption



Moisture permeates inward

Rate proportional to water activity gradient

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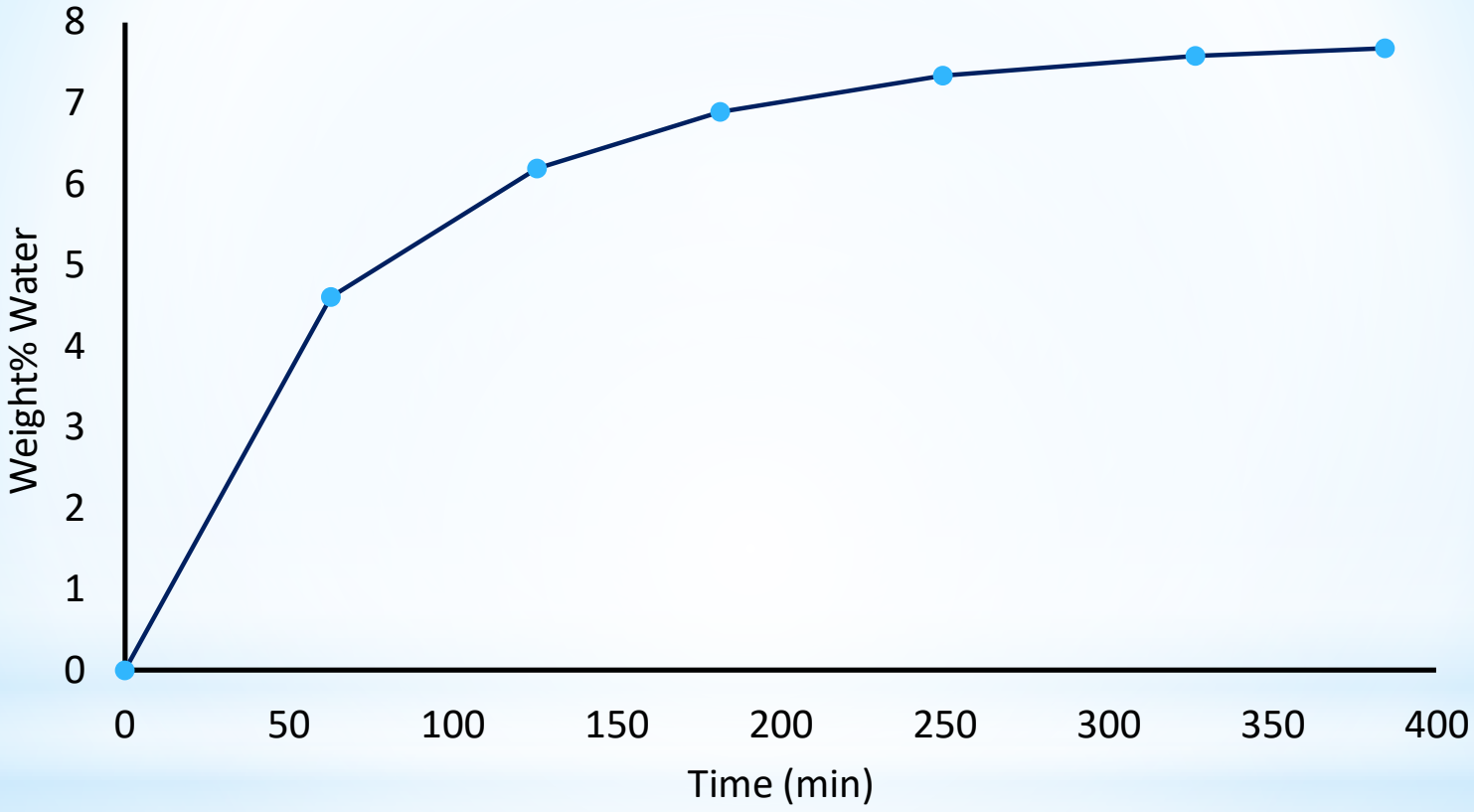
Example: Moisture uptake for tablet (99:1 MCC:Mg stearate) at 25°C/75%RH



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Approximation for Tablet Sorption

$$\frac{dRH}{dt} \approx k(RH_{ext} - RH)$$

$$RH_t \approx RH_{ext}\left(1 - e^{-kt}\right)$$

$$or \;\; k = \frac{\ln(RH_{ext} - RH_t)}{t}$$

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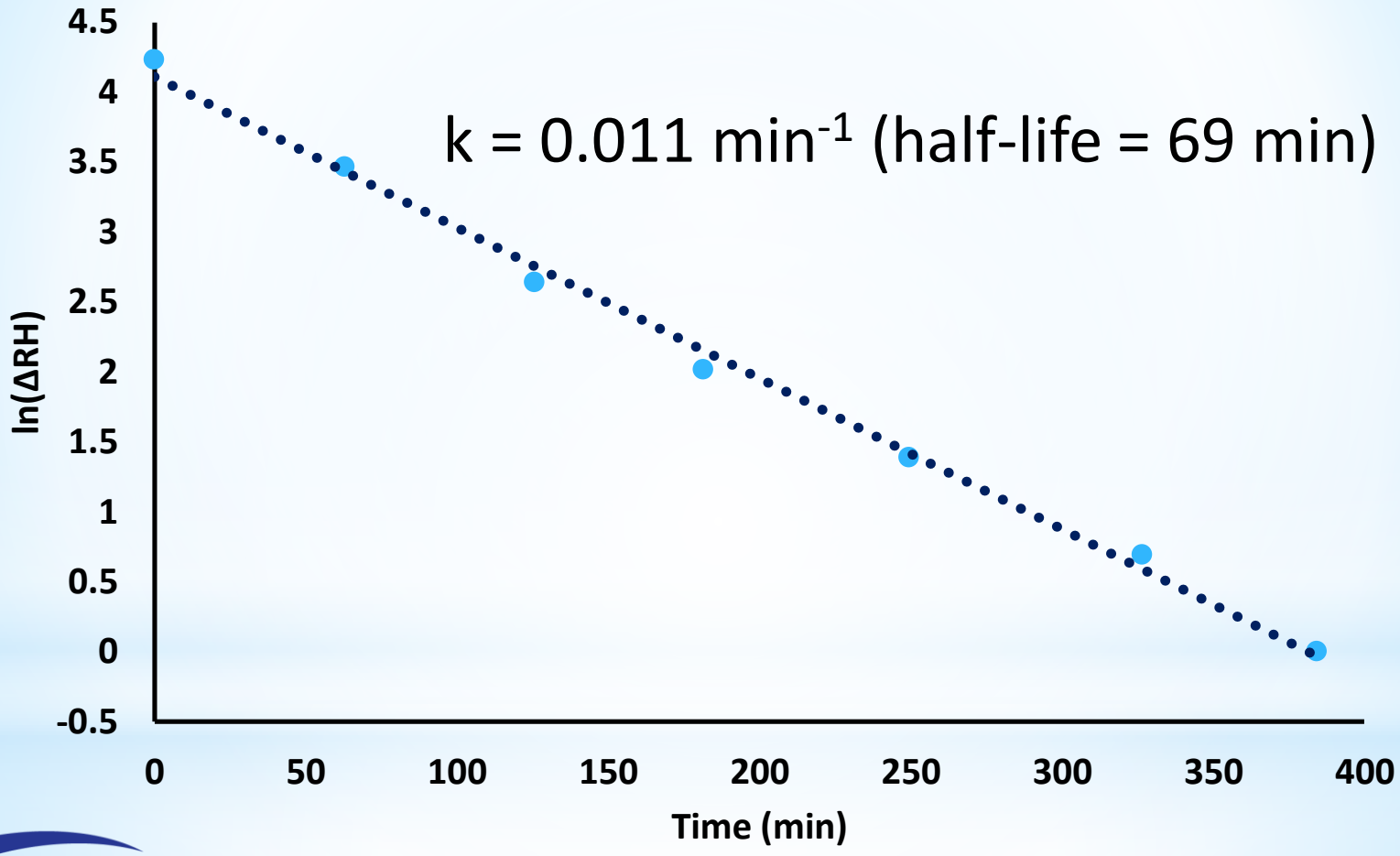
Tablet Moisture Sorption—Rate Transformation



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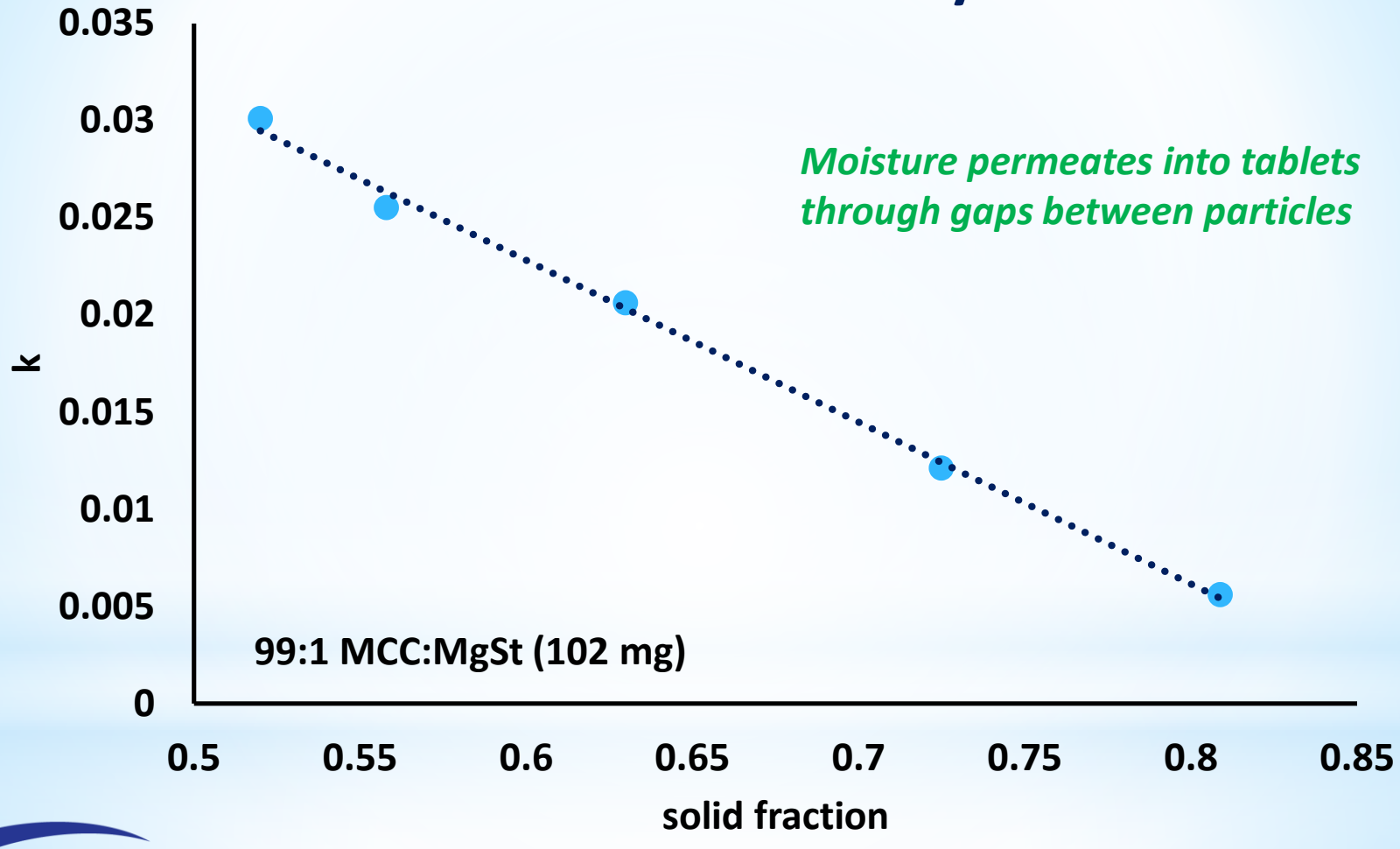
Moisture Sorption Rate Depends Directly on Tablet Density



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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 studies

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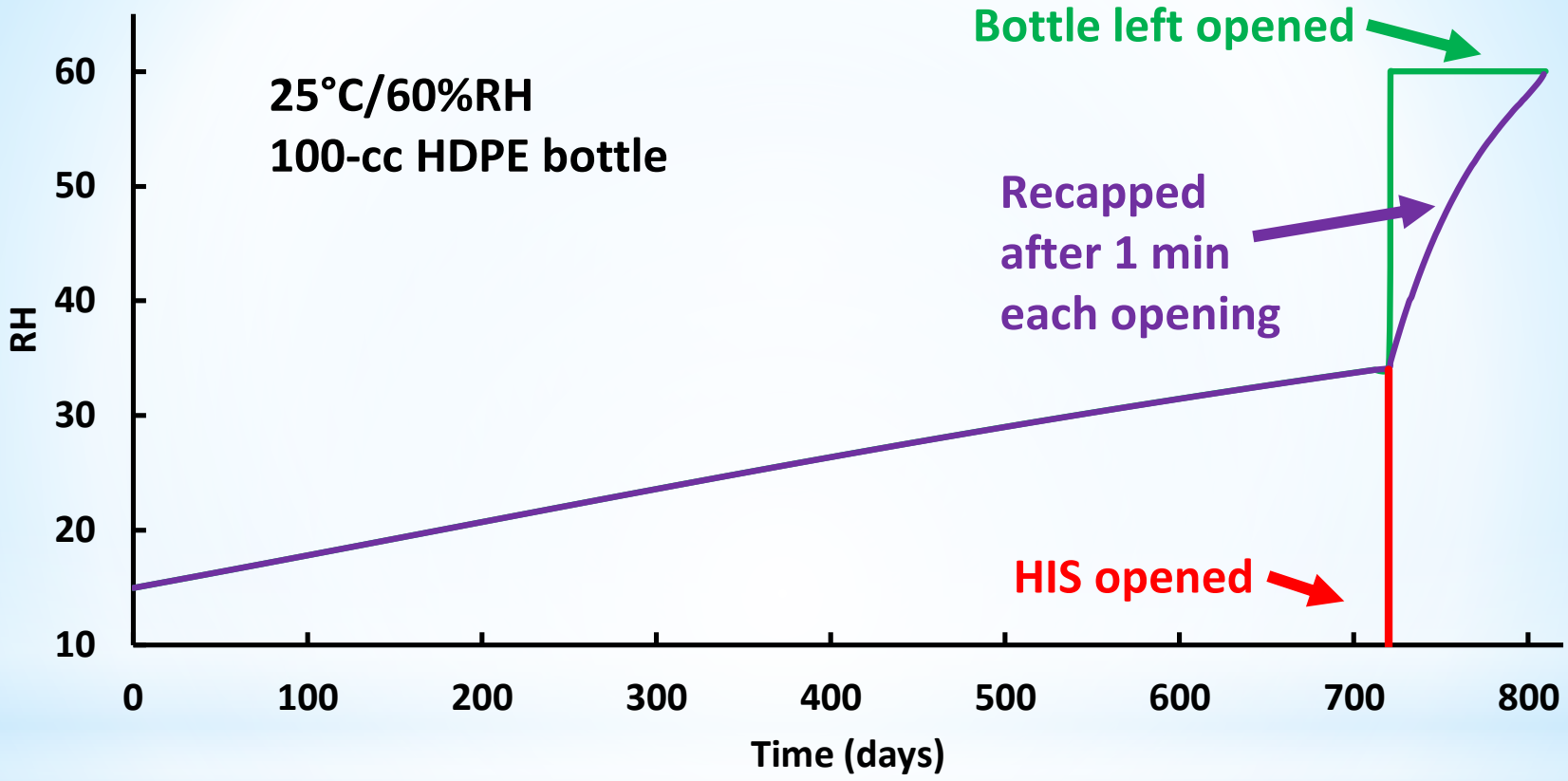
RH Consequences—Example



90 102-mg tablets (99:1 MCC:MgSt); 1 tablet/day removed

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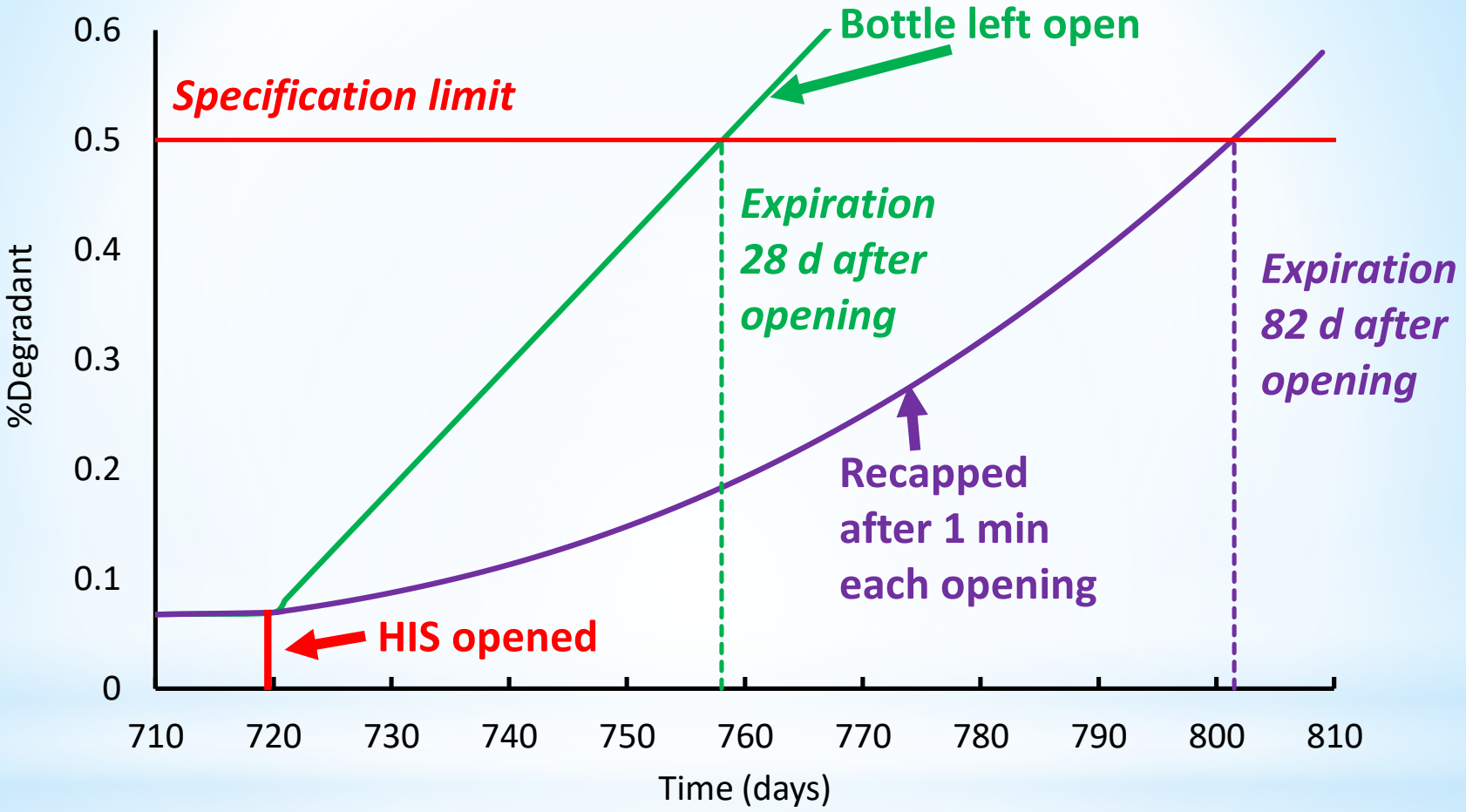
Stability Consequences: Example



ln A 27.5, E_a 23 kcal/mol, B 0.08

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Background—Excursions

- ICH defines storage conditions
  - US/Canada 25±2°C/60±5%RH
- Shelf-life = time packaged product remains safe + effective at storage conditions
- When conditions go outside range, need to determine impact of **excursion**
  - Still acceptable as labeled
  - Re-date
  - Discard

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Excursions

- Data loggers provide T (RH) data on product shipments
- When outside ICH specifications, is product still acceptable?

- ***Health Canada***
  - *Health Products and Food Branch Inspectorate GUIDE-0069 Guidelines for Temperature Control of Drug Products during Storage and Transportation 3.1.4*

All excursions outside the labelled storage conditions must be appropriately investigated and the disposition of the stock in question must be evidence-based (for example, stability data and technical justification).

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Excursions—I Low Temperature for Solids

- When temperature reduced abruptly for solids, can get condensation
- Results in powder clumping, capsule/tablet sticking together
- Condensation occurs when T drops below dew point

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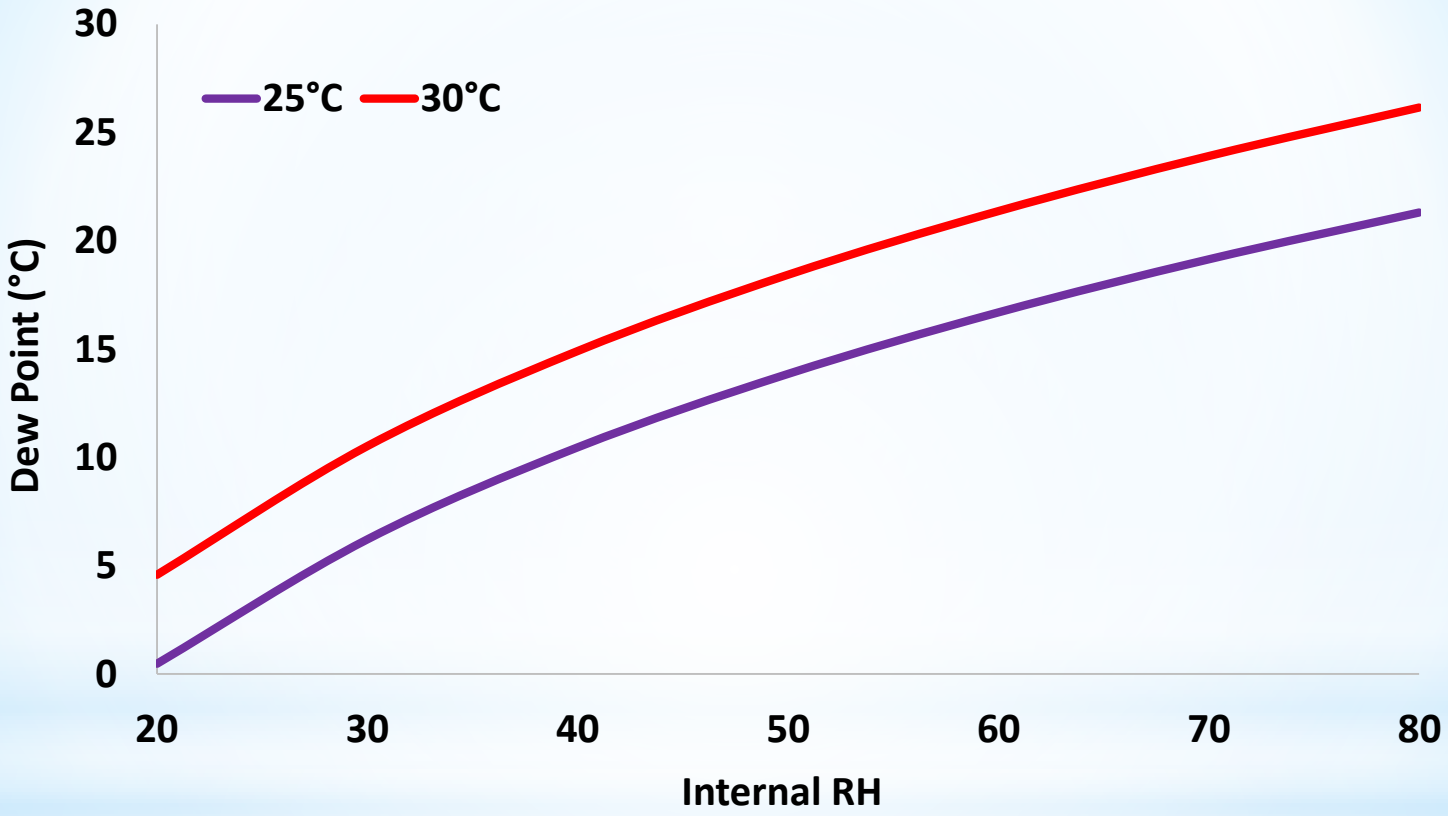
Dew Points



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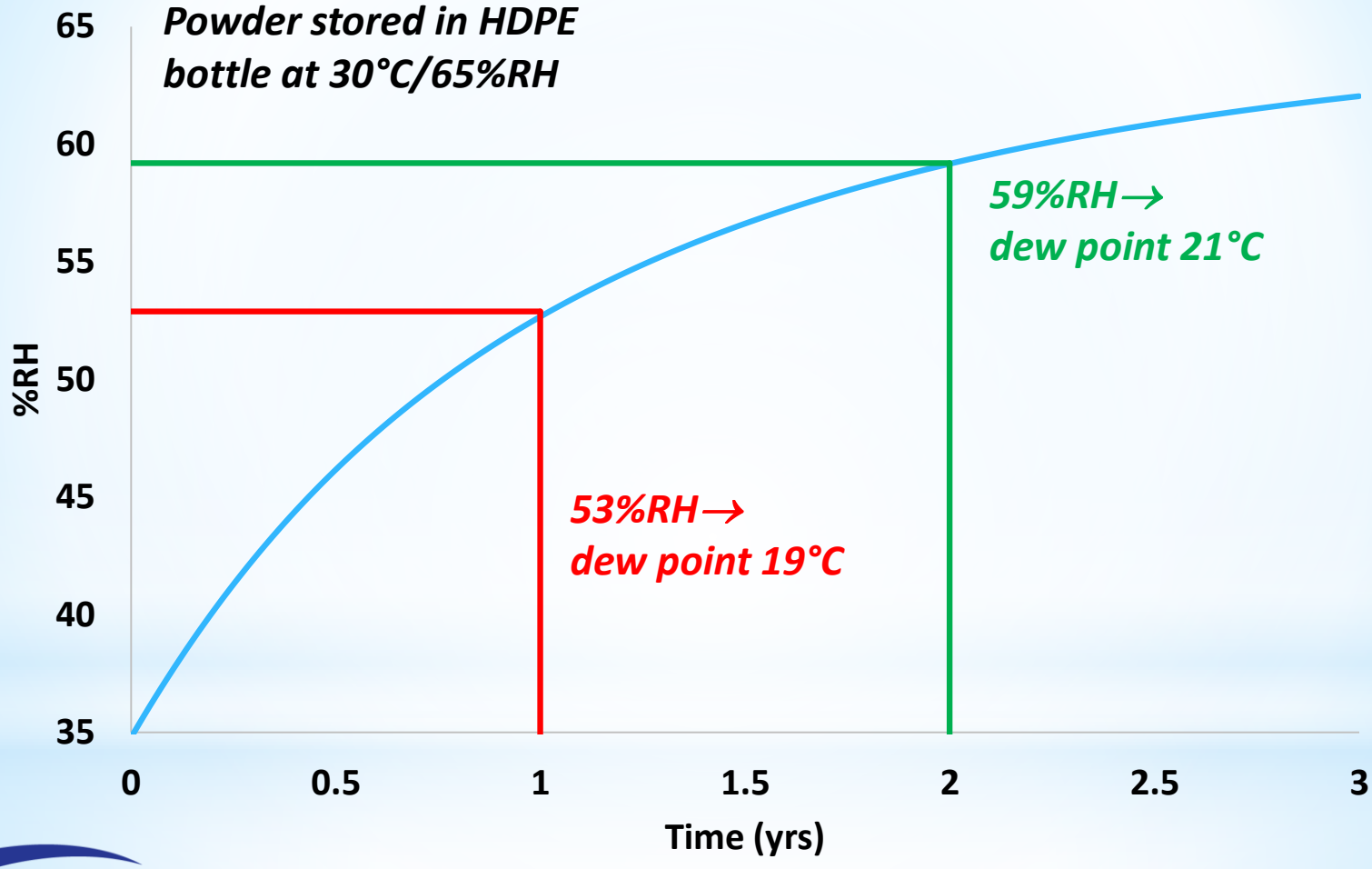
Condensation Calculation using ASAP*prime*® Plus Dew Point: Example (Condensation: T ≤ Dew Point)



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Excursions—II High Temperature for Solids

- Common practice (1): show that exposure to condition does not change degradant level (for example)
- Problems with this approach
  - Change may not impact end of shelf-life
  - Change may not be detected yet in fact change shelf-life
  - Age of product when excursion occurs can influence impact of excursion
  - Often do not have data as high a temperature as the excursion

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Excursions—II High Temperature for Solids

- Common practice (2): calculate the Mean Kinetic Temperature (MKT) and provide data at that temperature
- MKT adjusts the impact of higher temperatures based on the activation energy

$$MKT = \frac{E_a/R}{-ln\left(\frac{\sum_{i=1}^{n} t_i e^{E_a/RT_i}}{\sum_{i=1}^{n} t_i}\right)}$$

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Issues with MKT Approach

- Often calculated with assumed E_a
- Ignores impact of RH due to excursion
  - Direct from change in RH during excursion
  - Indirect from change in packaging moisture permeability with temperature

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ASAP*prime* Modeling Approach

1. Use ASAP on drug product to establish fitting behavior (sensitivity to temperature and RH)
2. Use data-logger information to calculate impact of excursion taking account
   a. Product age at the excursion point
   b. Change in internal RH
   c. Change in T
3. If ≥95% confidence still passes at end of shelf-life, product is acceptable 

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Example of ASAP*prime*® Model Approach

- 30 tablets in 60-cc HDPE bottle + 1 g silica gel desiccant
- Stored at 25°C/60%RH
- Two-year assigned shelf-life for degradation to specification limit of 0.5%
- ASAP study showed E_a = 27 kcal/mol, B = 0.044
- After 60-days at 25°C/60%RH, product saw one week at 48°C/78%RH
- Is it still acceptable?

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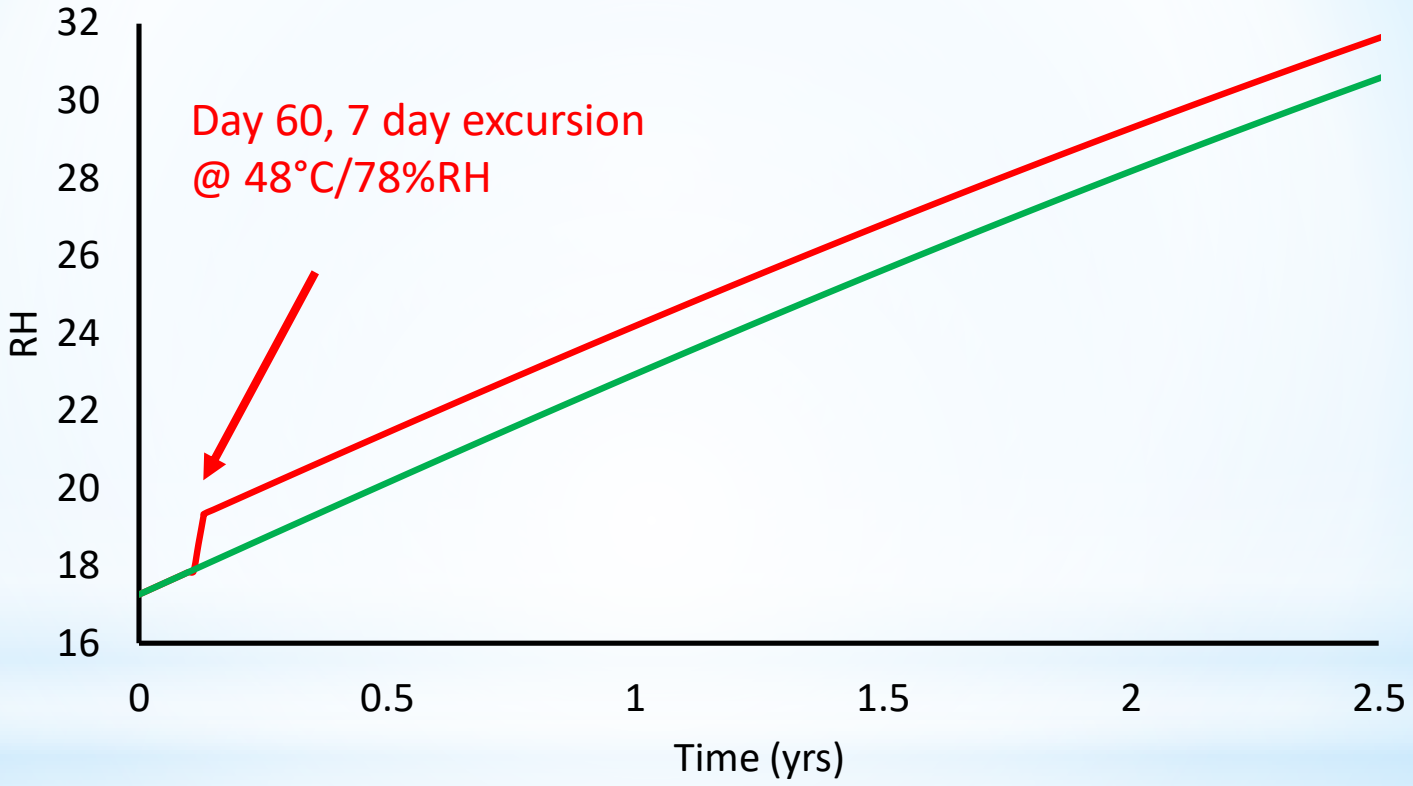
Example of ASAP*prime*® Model Approach



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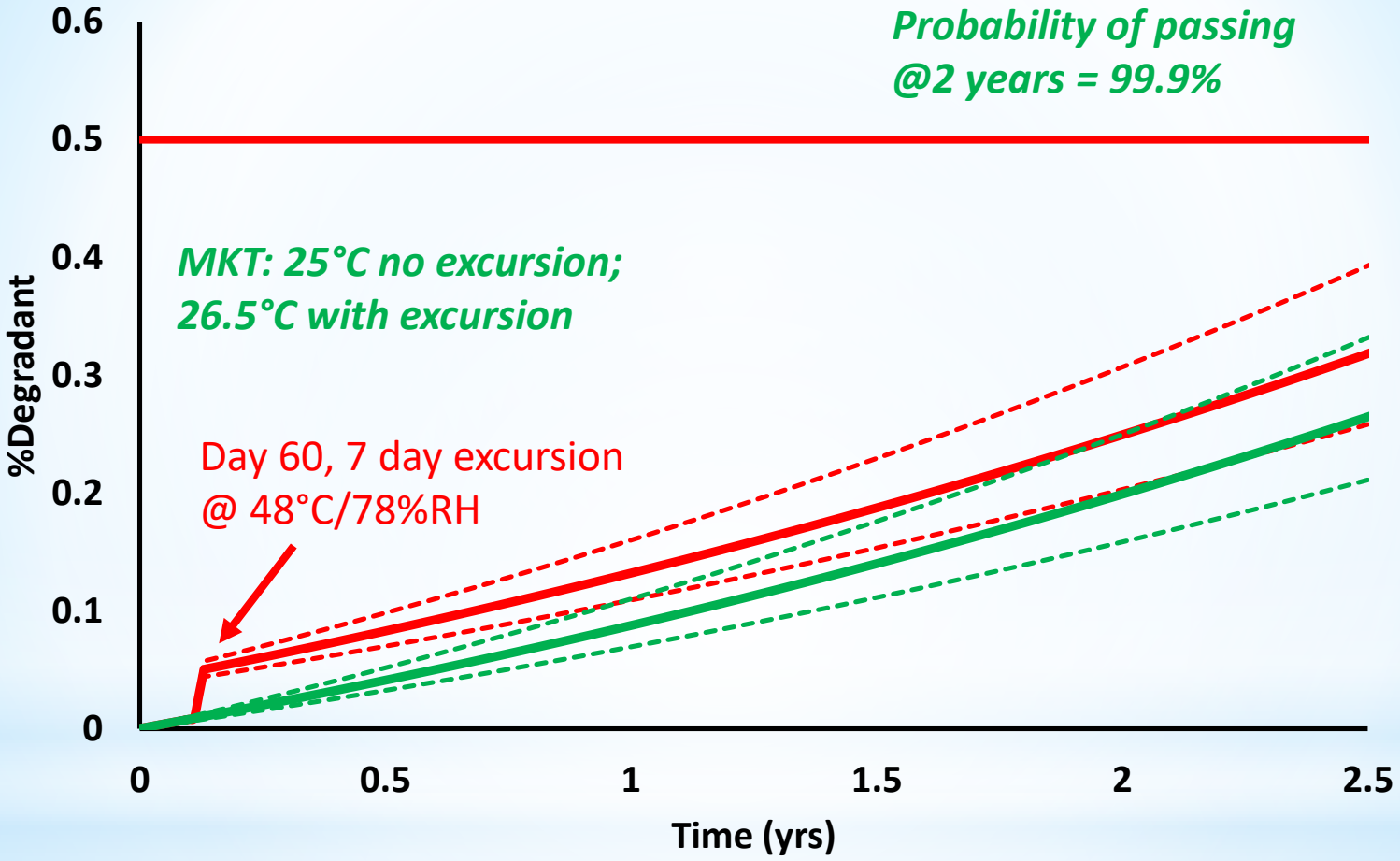
Example of ASAP*prime* Model Approach



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Example of ASAP*prime* Model Approach

- **Product still >95% confidence to pass: still acceptable as dated**
- **Note ASAP studies typically go up to 80°C, so excursion within design space**

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