



# **Accelerated Stability Assessment Program (ASAP)**

Anthony J. Carella

Director, Pharmaceutical Sciences & Manufacturing Statistics  
Pfizer Global Research and Development



# ASAP Presentation Outline

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- Arrhenius Modeling
- Oven Setup (DoE)
- Regression Method
- Monte Carlo Simulation
- Chemical Assumptions
- Packaging
- Summary



# Arrhenius Equation

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$$k(T) = A \times \exp(-E_a/[R \times T])$$

**T** = Temperature (K)

**R** = 1.987 (Molar Gas Constant, cal/mole-deg)

**E<sub>a</sub>** = Activation Energy (kcal/mole)

**A** = Frequency Factor

**k(T)** = Rate Constant at Temperature T



# Humidity-Corrected Arrhenius Equation

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$$k(T) \propto \exp(-E_a/[R \times T])$$

$$k(H) \propto \exp(B \times H)$$

$$k(T, H) = A \times \exp(-E_a/[R \times T] + [B \times H])$$

**H** = Relative Humidity (%)

**B** = Strength of Humidity Effect

**k(T, H)** = Rate Constant at Temperature T and  
Relative Humidity H



# Applying DoE Principles

Estimate model coefficients:

- no T×H interaction term in humidity-corrected model
- ensure that T and H linear effects are not highly confounded
- use nearly-orthogonal experimental designs for two factors (time variable has no statistical effect on appropriateness of design)

Temperature (degrees C)	Relative Humidity (%)	Time to Last Pull (days)
.	.	0
80	40	2
70	75	1
70	5	14
60	40	14
50	75	14

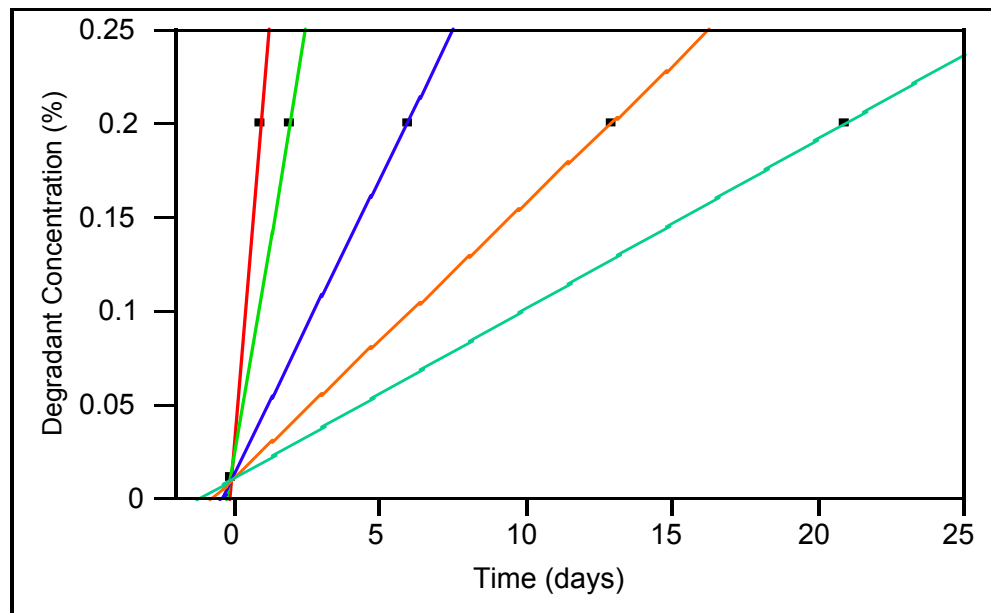


# Double Regression Method

**STEP 1:** Fit “Zero-order” Kinetic Regression of the Concentration of an Impurity vs. Time, at each Temp/RelHum Condition:

$$C(T, H, t) = d + k_0(T, H) \times t$$

Fitted Degradation Rates at each ASAP Storage Condition



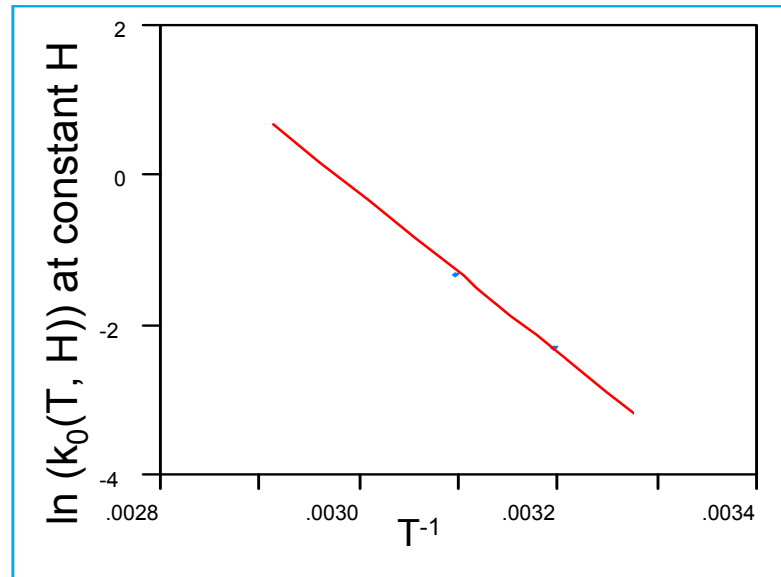


## Double Regression Method

**STEP 2:** Fit “Modified Arrhenius” Regression, using fitted  $k_0(T, H)$  [Slope] values from Kinetic Regression in Step 1:

$$\ln(k_0(T, H)) = A - E_a/(R \times T) + B \times H$$

Predicted Degradation Rates at any Temperature, keeping % RH Constant





## Objective: Point Estimates and Ranges

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Estimate the true median and provide a prediction interval for:

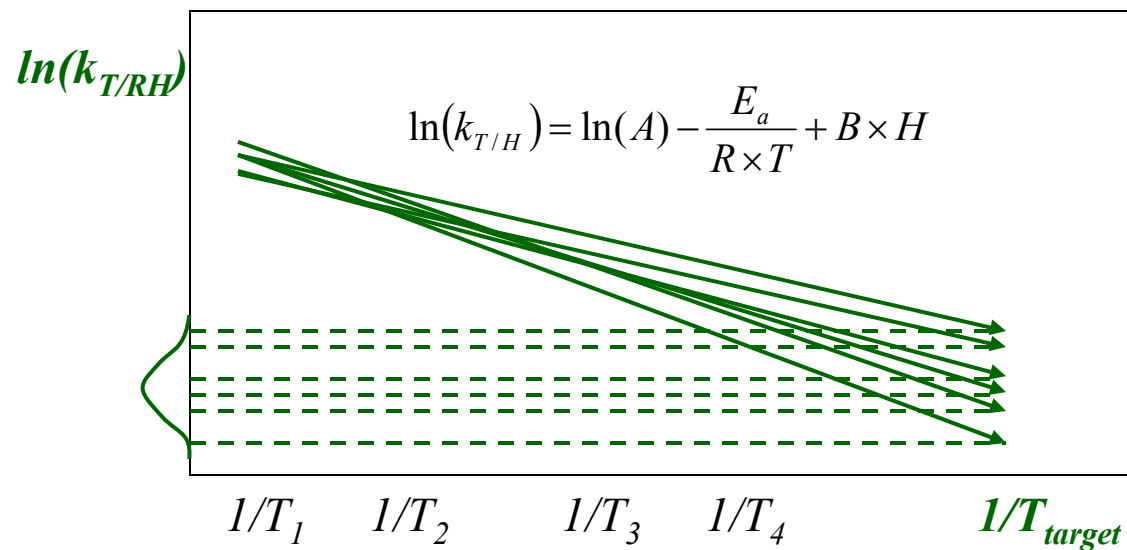
- modified Arrhenius parameters ( $A$ ,  $E_a$ ,  $B$ )
- shelf-life at each desired temperature/RH storage condition (e.g., 30C/75RH)

using Monte Carlo simulation.



# Monte Carlo Simulation

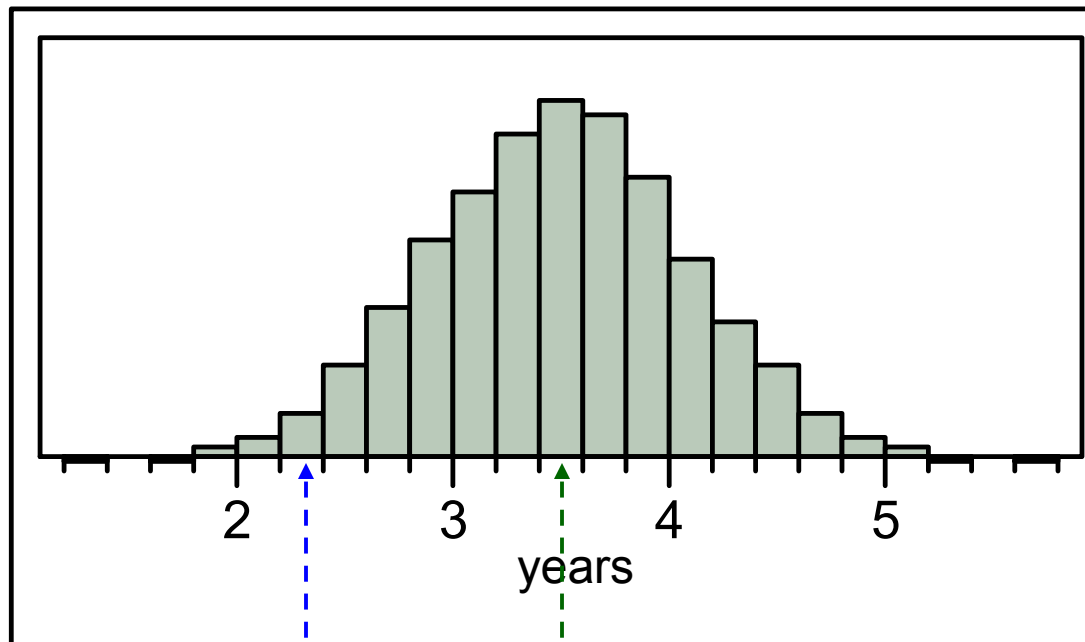
- 5000 ASAP experiments are simulated (new data for each time pull at each storage condition)
- Step 1 and 2 regressions are fit during each round of Monte Carlo simulations
- Allows 5000 simulated sets of  $A$ ,  $E_a$ , and  $B$  to be created





# Monte Carlo Simulation

- Point estimates and ranges for A,  $E_a$ , and B are calculated from the 5000 simulated sets.
- Point estimates and ranges for room temperature shelf life are calculated from the 5000 simulated sets.



90% lower prediction interval (2-sided)

2.35 years

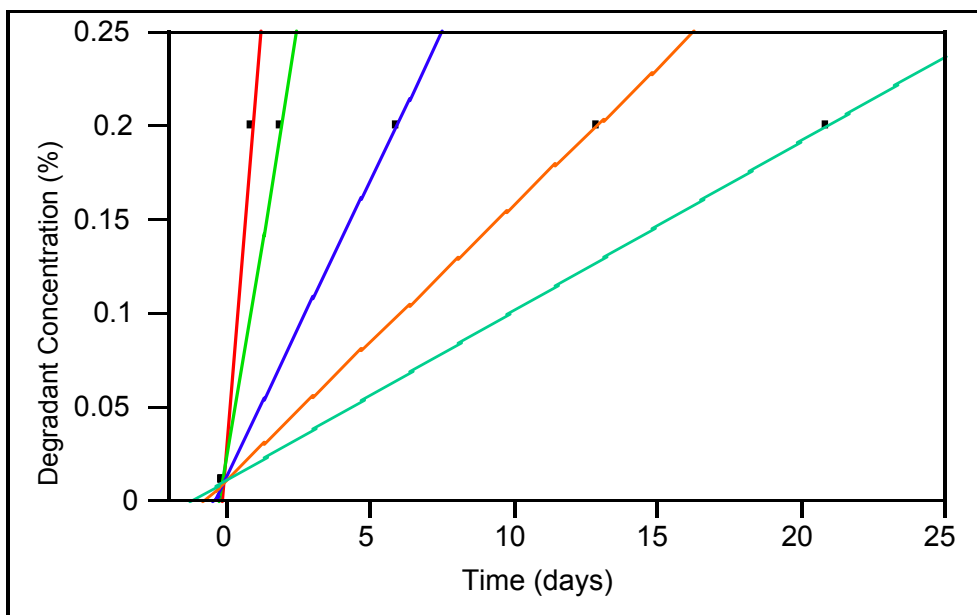
estimated shelf-life median

3.62 years



# Chemical Assumptions

- First Assumption: at low levels, chemical degradation (conversion) can be approximated by zero-order kinetics
- Second Assumption: Isoconversion Paradigm



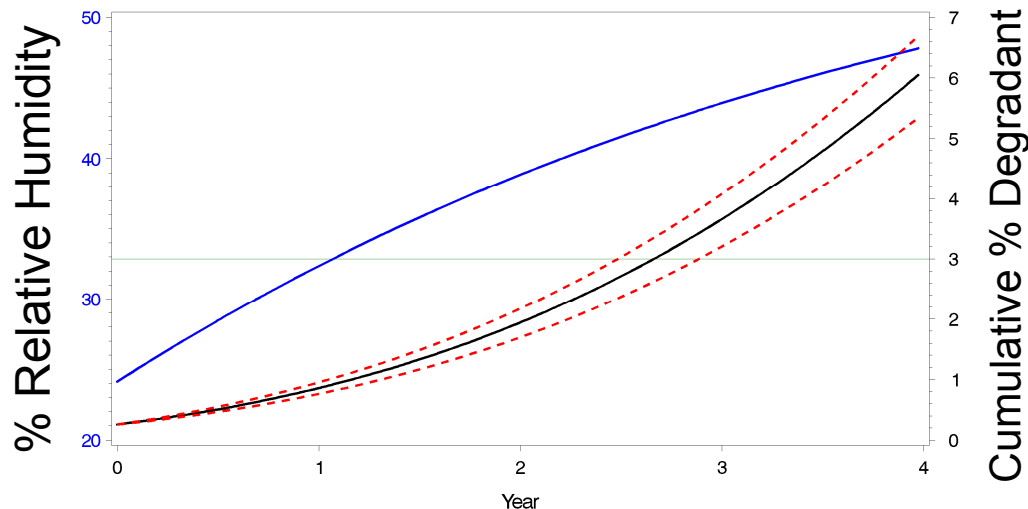


# Degradation in Packaging

v1

Additional information needs to be incorporated into the model to derive predictions for packaged tablets:

- Package Moisture Vapor Transmission Rate
- Total Tablet Weight and Tablet Equilibration RH
- Excipient Properties
- Desiccant Type and Weight



Modeling % Relative Humidity and Cumulative % Degradation, in Packaging



## ASAP Advantages

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- Faster than traditional Accelerated Aging studies (2 or 3 weeks, versus 6 to 12 weeks)
- Imprecision in estimates is quantified (through Monte Carlo simulation)
- Leads to increased understanding of degradation mechanisms
- Degradation within a package can be modeled (and imprecision in estimates can be quantified, again through Monte Carlo simulation)



# Acknowledgements

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