Case Studies: Applying Accelerated Stability Assessment Program (ASAP) to Excursions, Formulation and Process Changes

Garry Scrivens PhD, Pfizer

Science of Stability Conference
Dublin 2017

Outline

- Present examples of how accelerated stability data can be used to predict the effect of:
  - Excursions (both temperature and humidity)
  - Formulation changes
  - Processing changes

Temperature Excursions
(unplanned deviations from the intended storage temperature)

- ASAP is applicable only to chemical degradation processes
- Also need to consider physical changes that could occur as a result of high / low temperatures
  - E.g. melting, glass transitions, form changes, water condensation, etc.
  - The effect on dissolution

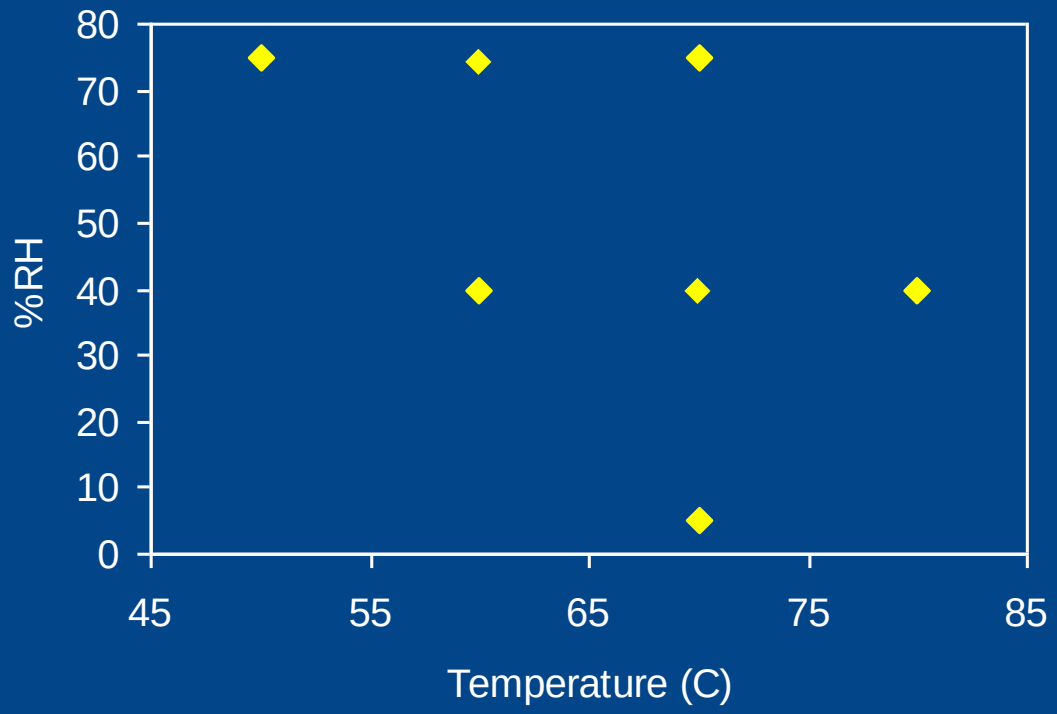
Application of ASAP to Temperature Excursions

- What is “ASAP”
  - Accelerated Stability Assessment Program
  - It is a study into the effects of temperature and humidity on a sample
  - Carried out on unpackaged samples
  - Elevated temperatures are used in order to accelerate the study (optional!)
  - The effects of temperature and humidity are modelled so that the degradation rate under any temperature / humidity condition can be predicted by extrapolation / interpolation

Example ASAP Study

Check physical properties of API and excipients to ensure that the degradation under accelerated conditions is representative of long-term behaviour)

Temp (ºC)	Relative Humidity (%)	Duration (Days)
70	75	1, 2
70	40	4, 7
60	75	4, 7
80	40	1, 2
70	10	14, 21
60	40	14, 21
50	75	14, 21

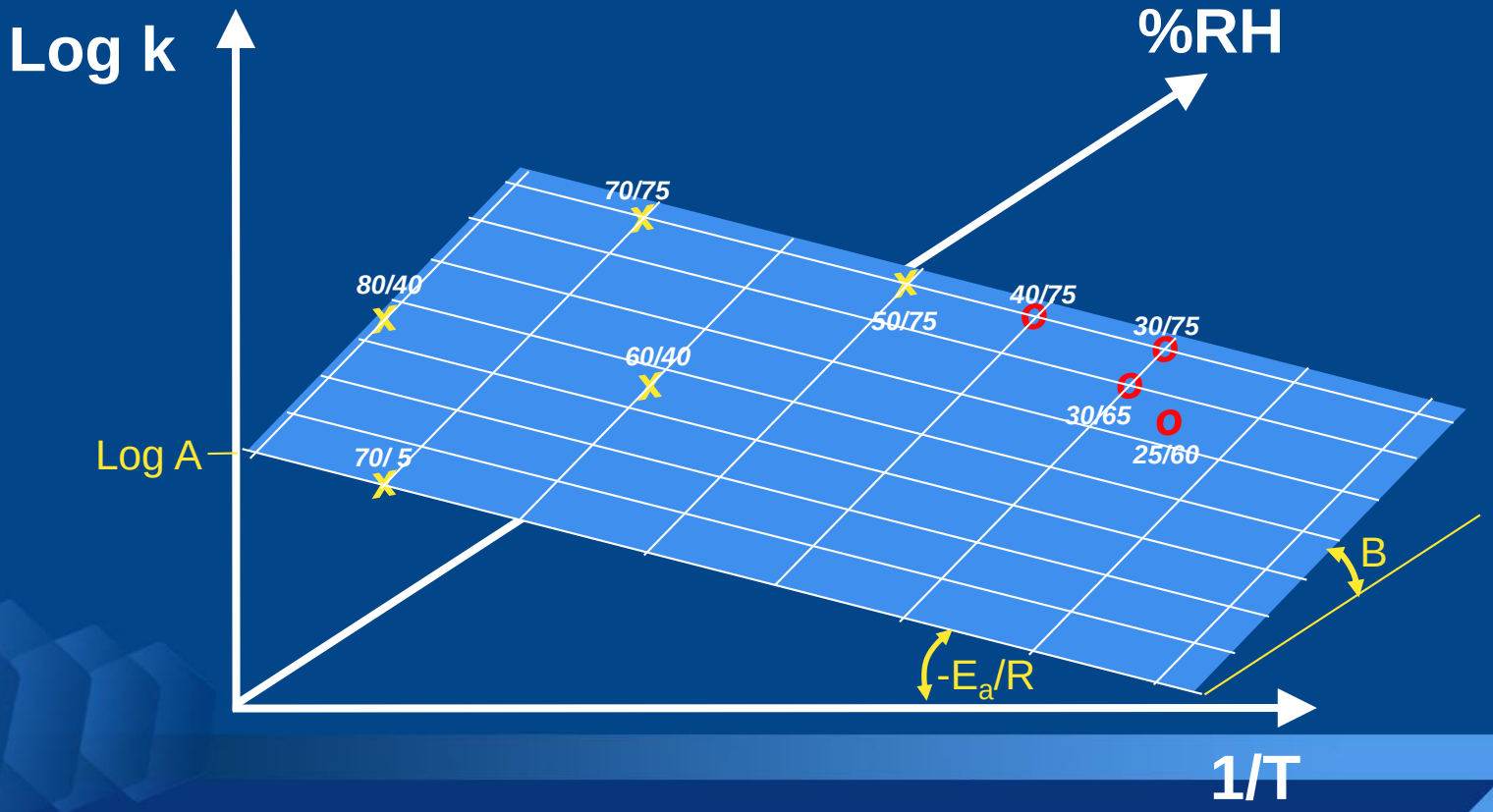


Typically use HPLC to measure the % degradation at each timepoint

Modelling the ASAP Data

Measure k (e.g. k = Degradation growth / time)

$$\text{Log } k = \text{Log } A - E_a/R(1/T) + B(\%RH)$$



Application of ASAP to Temperature Excursions – "Proof of Concept" Case Studies

Product A

Temp (ºC)	Relative Humidity (%)	Duration (Days)	%Deg Deg Prod C
70	75	2	0.455
70	40	2	0.37
60	75	2	0.195
80	40	1	0.48
70	11	11	0.315
60	40	11	0.29
50	75	14	0.325
Calculated regression coefficients:		Ln A: E_a: B:	41.91 31.01 0.034

Product B

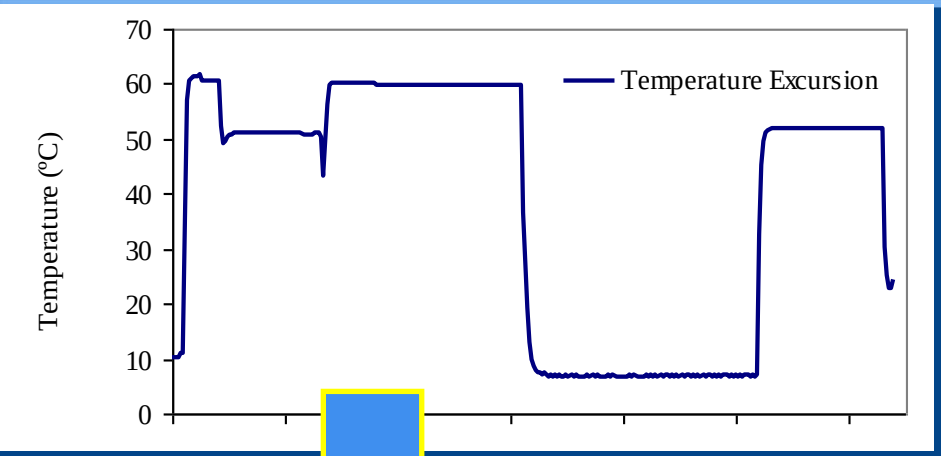
Temp (ºC)	Relative Humidity (%)	Duration (Days)	%Deg	
			Deg Prod D	Deg Prod E
60	50	52 hours	3.97	0.85
60	29	7	2.35	0.90
50	51	8	3.56	0.66
50	31	8	1.06	0.34
Calculated regression coefficients		Ln A: E_a: B:	38.28 27.36 0.071	41.97 29.92 0.044

Application of ASAP to Temperature Excursions – "Proof of Concept" Case Studies

- Simulated Temperature Excursion:
  - For both products, a sealed bottle containing 100 tablets was subjected to a number of temperature fluctuations over a 7 (& 13) day
  - At all times a data logger was kept in close proximity to the bottle, set to read the temperature every 30 minutes
- Can the amount of degradation occurring in these tablets be predicted solely on the basis of the data logger information and the ASAP study data?
  - The tablets were analysed after the excursion so that the actual true extent of degradation could be known and then compared to the predicted results.
- The water activity of the tablets was measured for both products: 0.5 for Product A and 0.3 for Product B

Application of ASAP to Temperature Excursions – "Proof of Concept" Case Studies

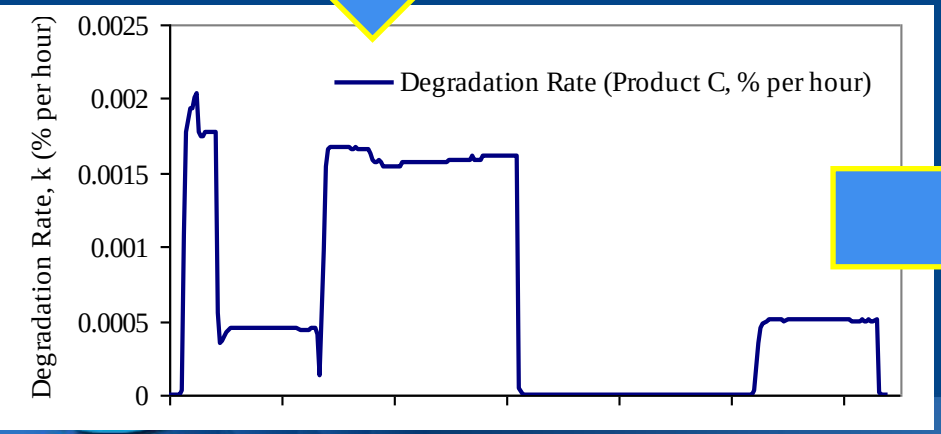
- Product A

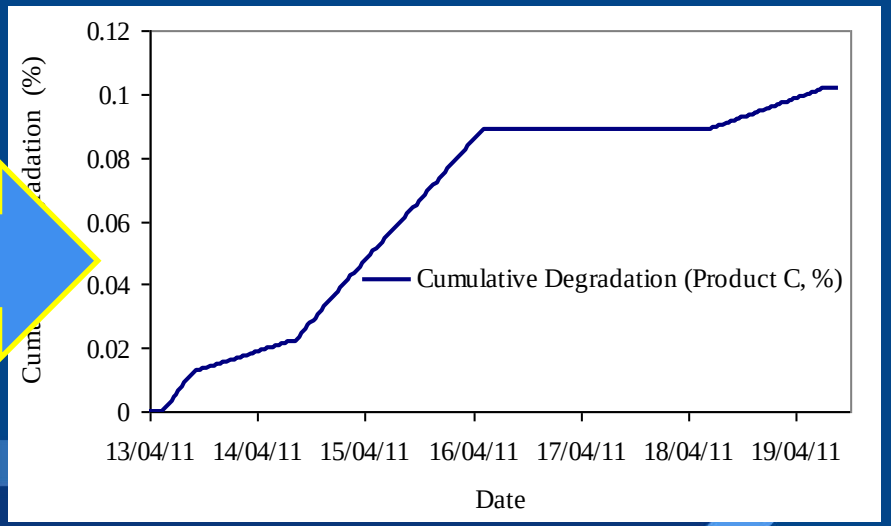


Data Logger Information

Degradation Rate = $A.\exp(-E_a/RT).\exp(B.RH)$

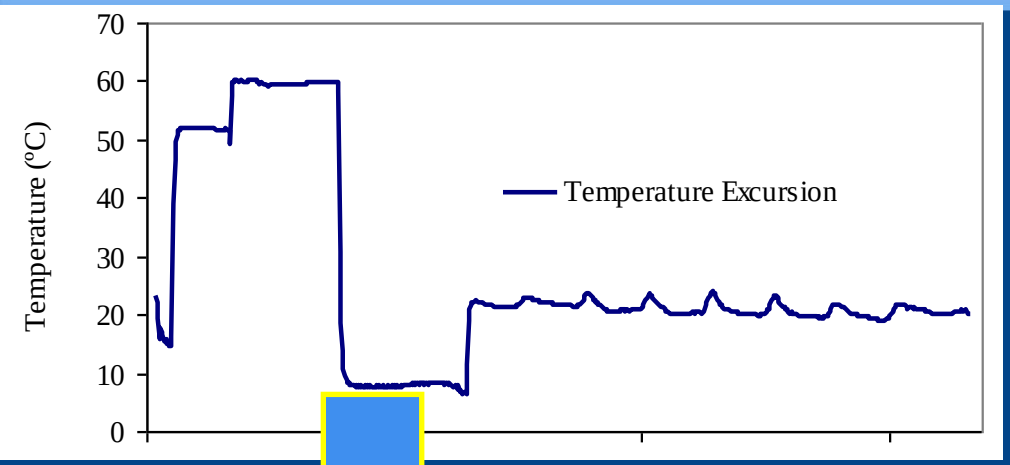
0.1% growth during excursion





Application of ASAP to Temperature Excursions – "Proof of Concept" Case Studies

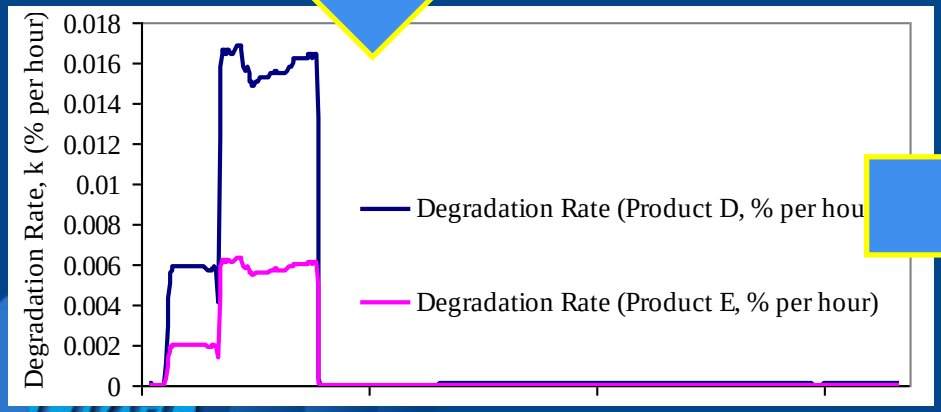
- Product B

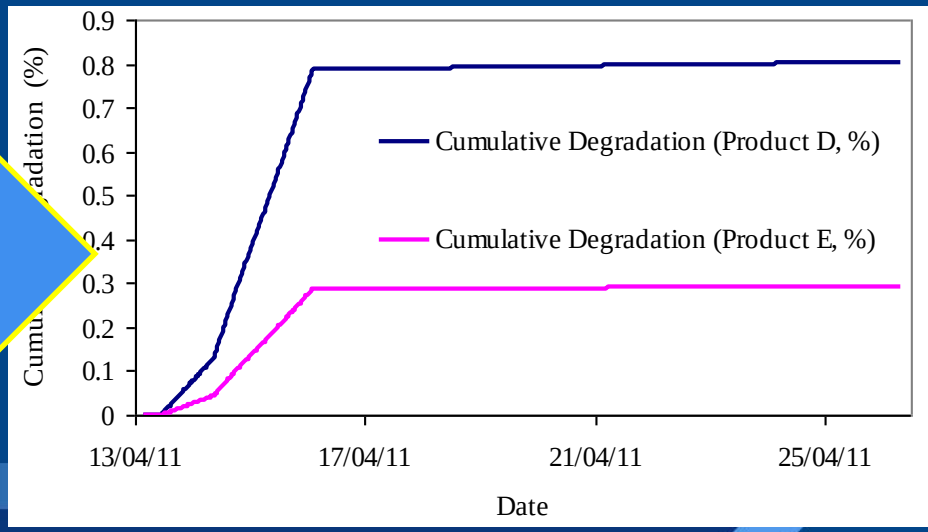


Data Logger Information

0.8% & 0.3% growth during excursion

Degradation Rate = $A.exp(-E_a/RT).exp(B.RH)$





Application of ASAP to Temperature Excursions – "Proof of Concept" Case Studies

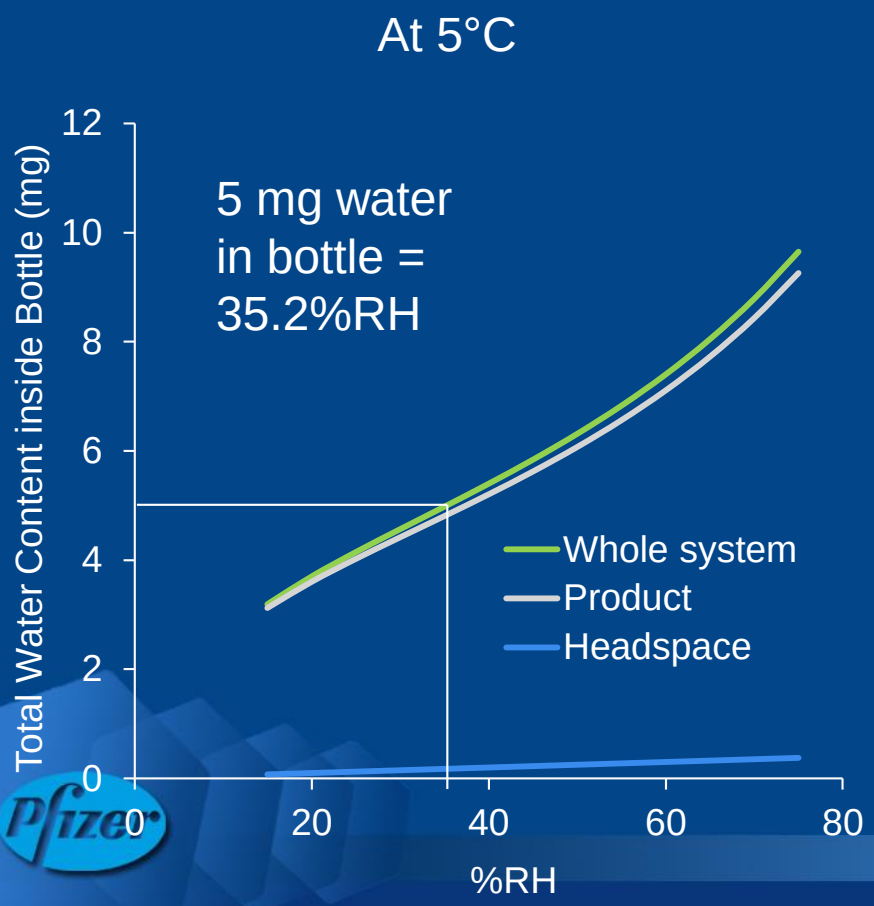
		Actual Result	Predicted Result
Case Study A	Degradation Product C	0.12	0.10
Case Study B	Degradation Product D	0.77	0.80
	Degradation Product E	0.26	0.29

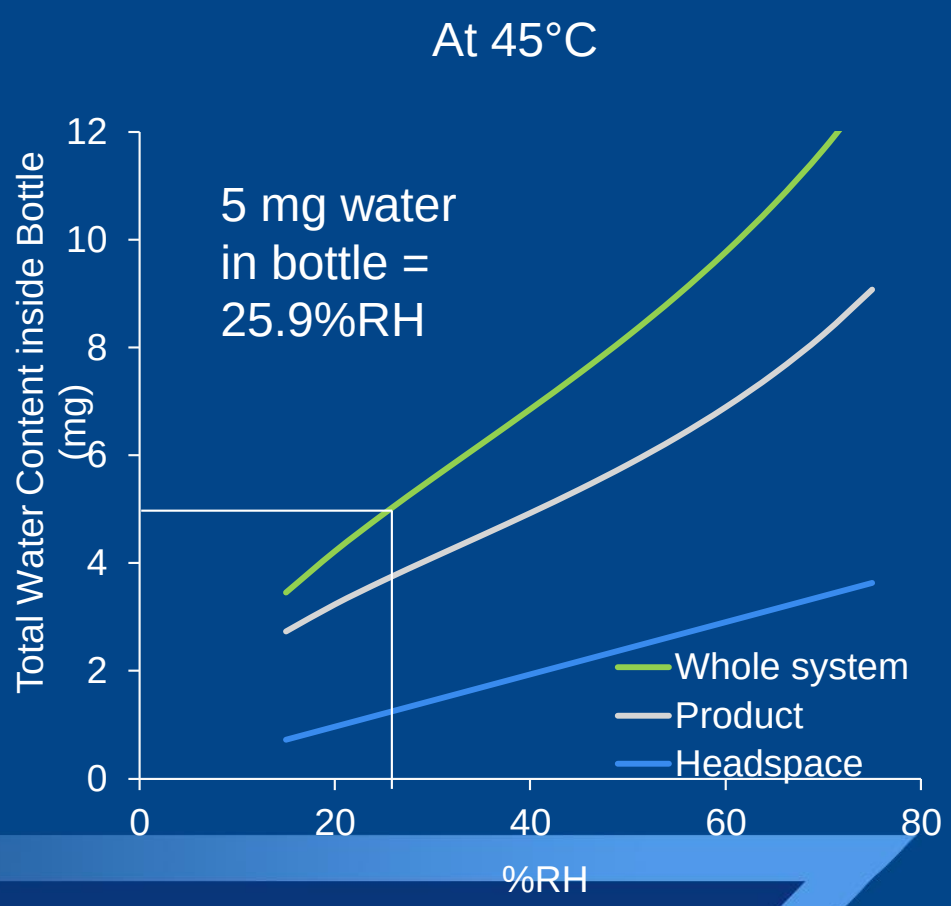
Approach appears to work with fluctuating temperatures

Temperature Excursions

Effect of Fluctuating Temperature on Humidity inside Packaging

1 small tablet in a 60 cc bottle

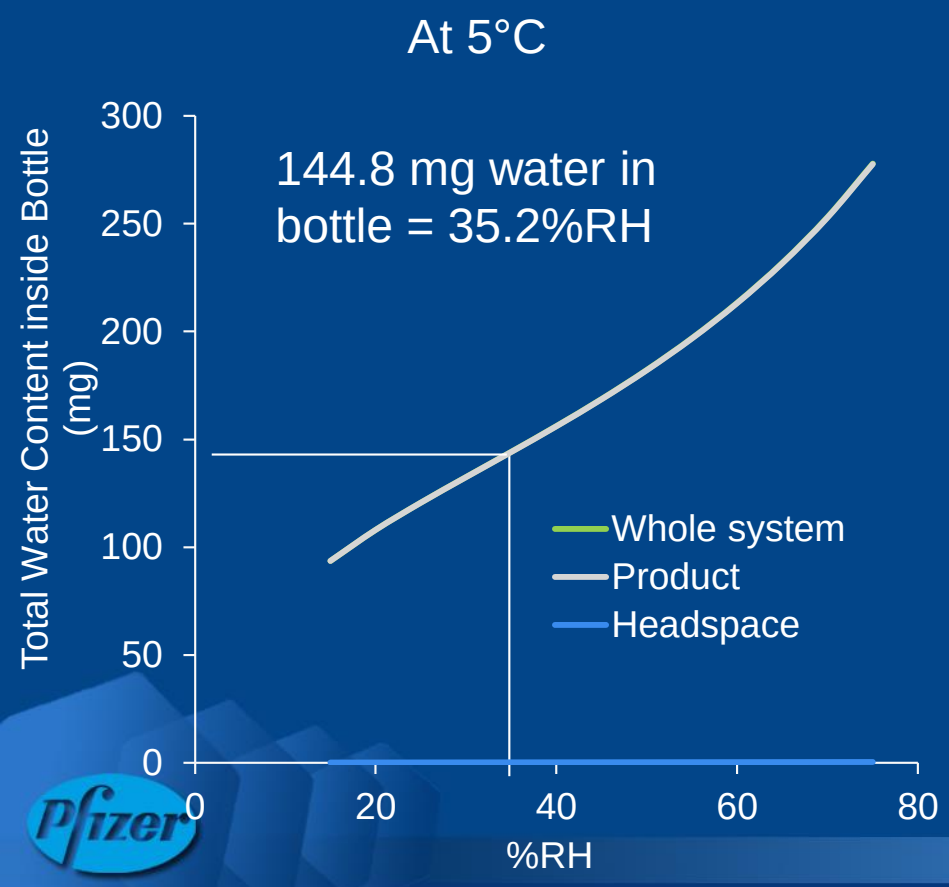


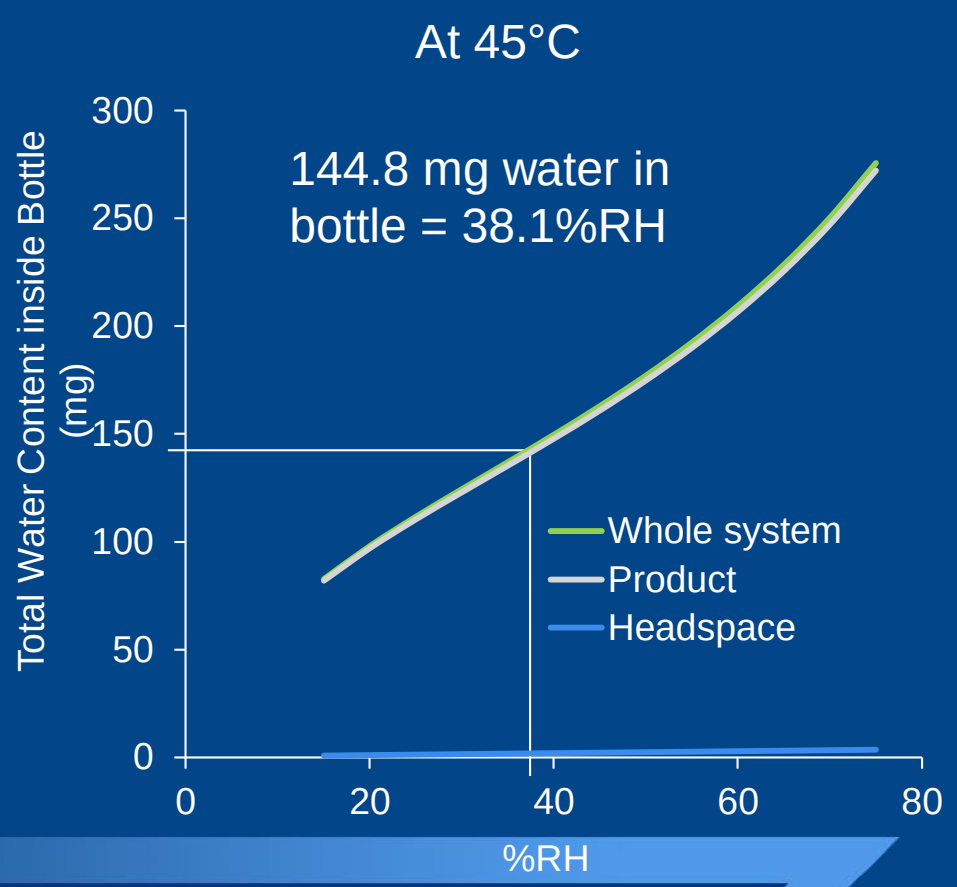


Temperature Excursions

Effect of Fluctuating Temperature on Humidity inside Packaging

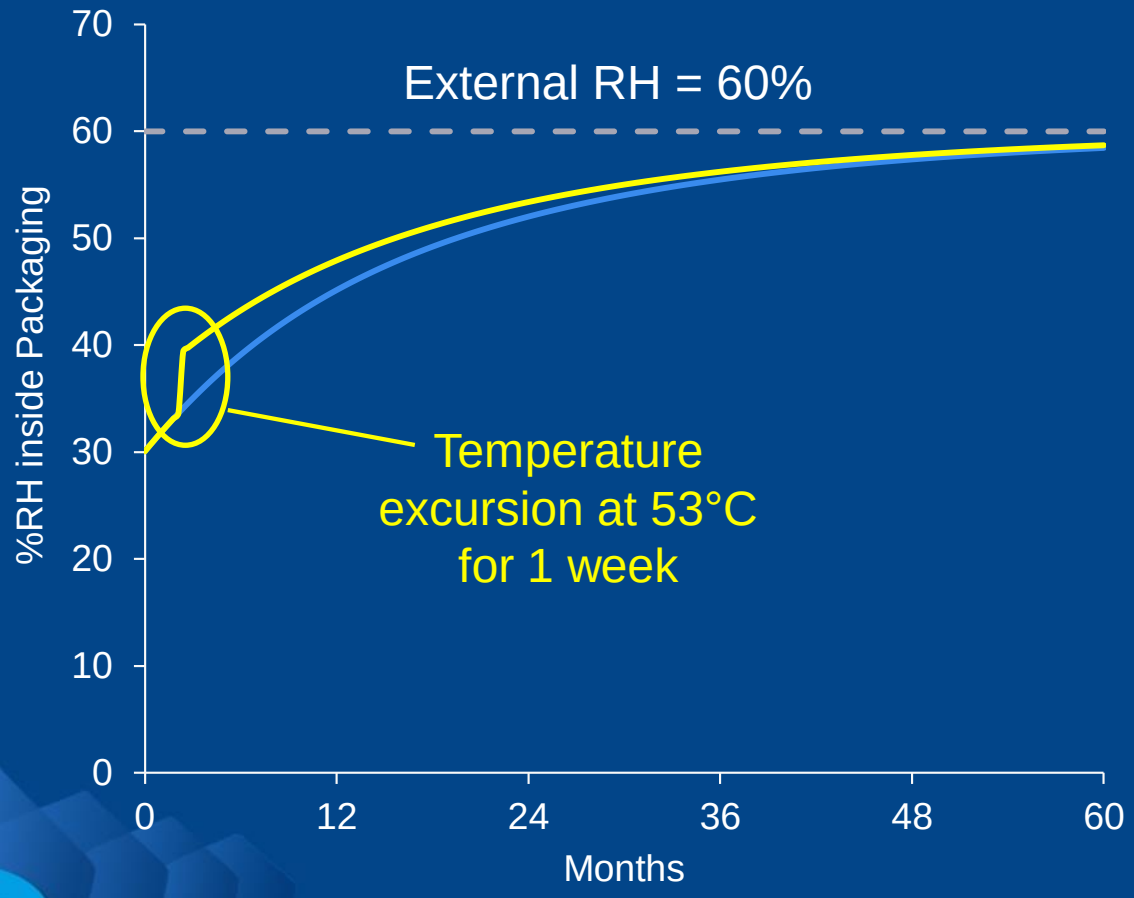
30 small tablets in a 60 cc bottle





Temperature…

…affects the moisture permeability of packaging

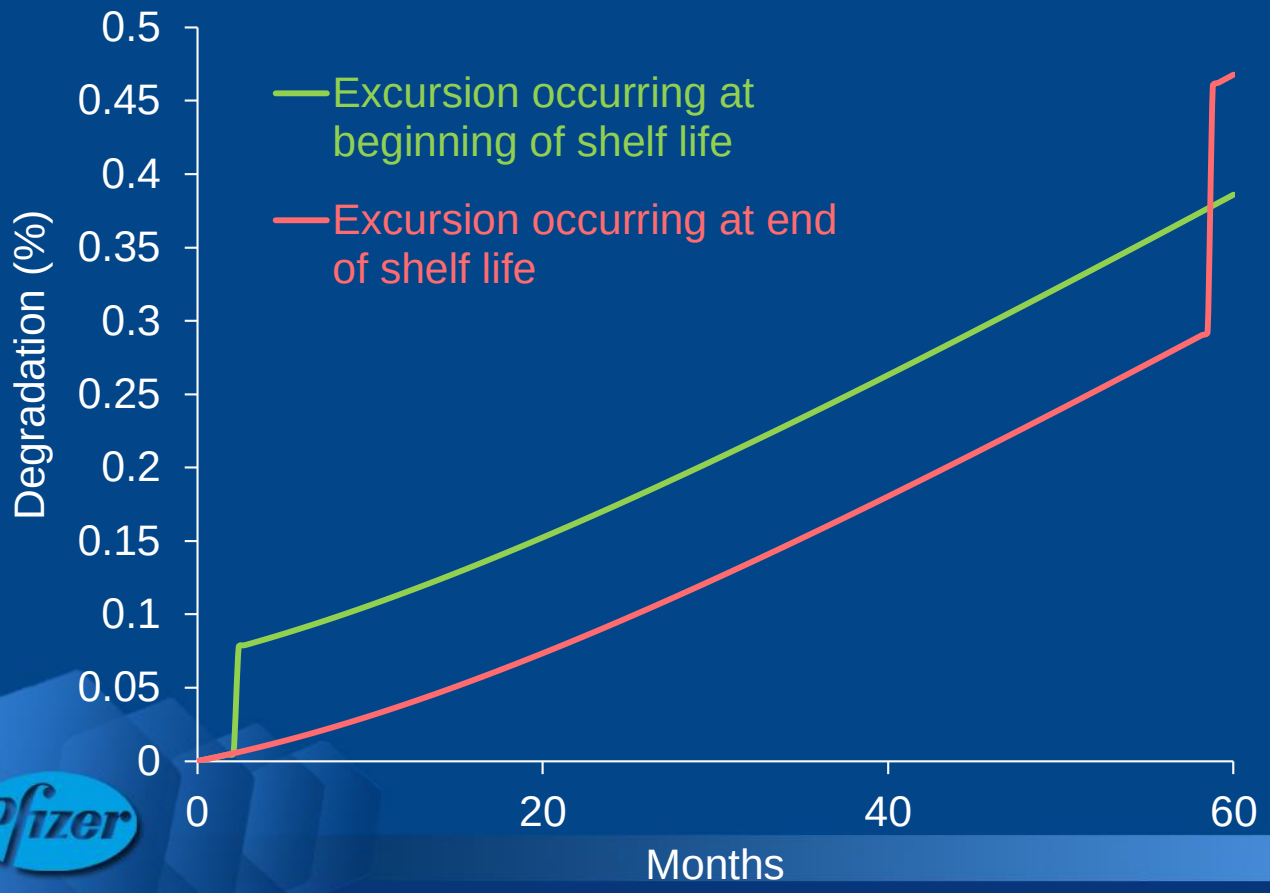


Average humidity in packaging (over 60 months) in scenario with temperature excursion = 52.5%RH

Average humidity in packaging (over 60 months) in scenario without temperature excursion = 51.2%RH

The impact of an excursion is affected by when it occurs in the shelf-life of the product

$$k = A \times \exp(-E_a/R/T) \times \exp(B.RH)$$



Why?

1. The humidity inside the packaging is generally higher at the end of shelf-life
2. The rate of degradation is affected by temperature and RH in a multiplicative way

Temperature Excursions
Some thoughts and practicalities

- Mean Kinetic Temperature (MKT)
  - An average temperature based on the Arrhenius Equation:

$$MKT = (E_a/R) / Ln \{ [e^{-E_a/RT_1} + e^{-E_a/RT_2} + \ldots + e^{-E_a/RT_n}] / n \}$$

  - Calculation of MKT requires E_a to be known
  - USP allows an assumed E_a of 20 KCal/mol for all products (this is rather low based on our experience from ASAP studies – underestimating E_a leads to an underestimation of the MKT)
  - ASAP provides actual E_a
  - E.g. If a product is exposed to an MKT of 40°C for 2 wks, but for the rest of its 2yr shelf-life it spends at an MKT of 25°C, the product's overall MKT for the 2 yr period is 25.7°C (E_a = 20 KCal/mol) or 26.2°C (E_a = 30 KCal/mol)
    - **Is this significant?** Within typical oven specification of ± 1°C of set temperature
  - The cumulative effect of multiple excursions…do we risk-assess excursion events in isolation? Do we record all excursions occurring to the same sample?

Temperature Excursions
Some thoughts and practicalities

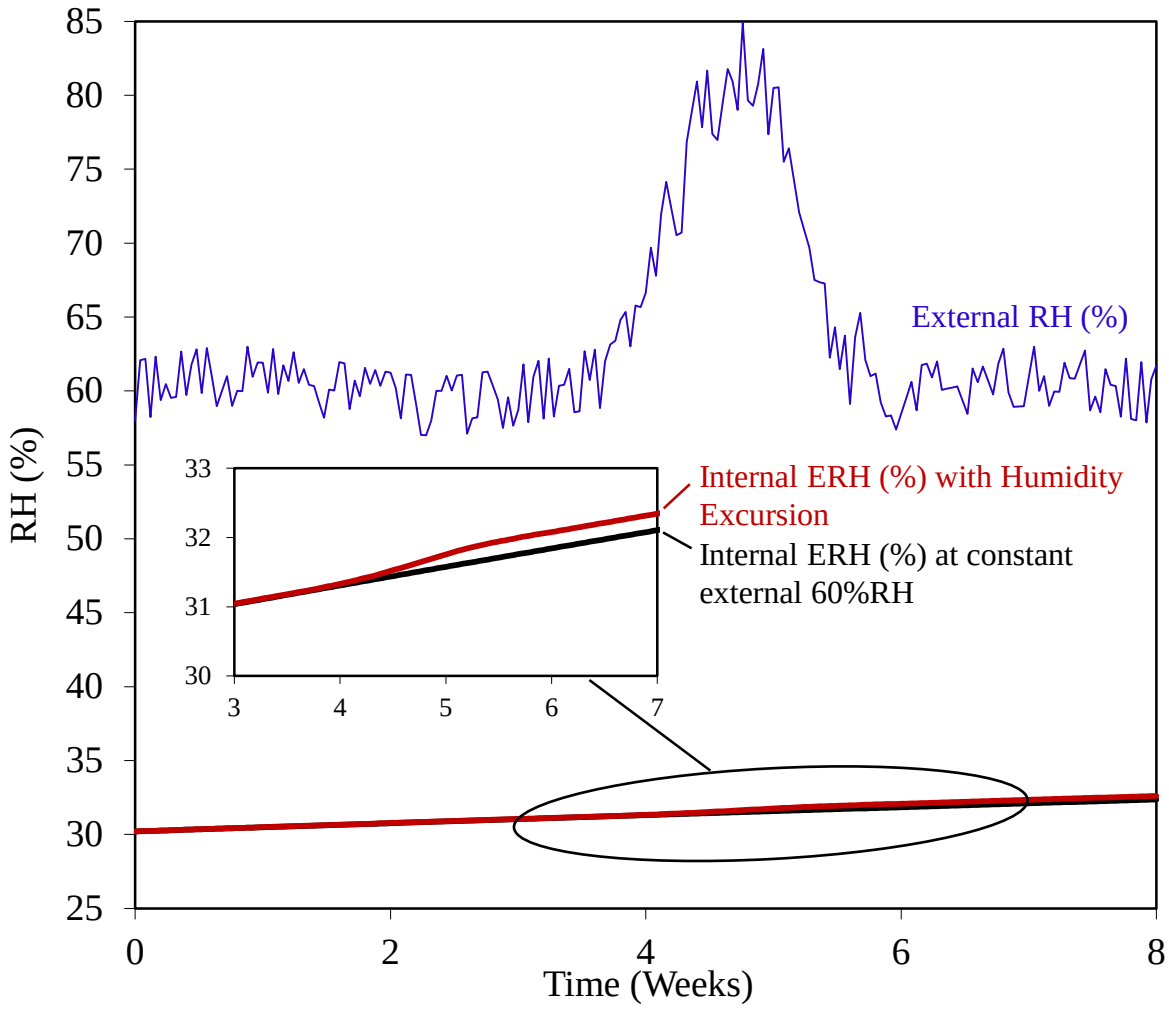
- Is this significant..?
- If a product has a 2 yr shelf life when stored at 25°C…
  - Then storage at a MKT >25°C will reduce the shelf life…
  - Rely on a certain ‘comfort margin’ in the set shelf-life?
- It is possible to use the same sort of calculations as MKT but render the conclusions in terms of by how much the shelf-life has been shortened as a result of the excursion…
  - E.g. Case Study A: MKT over 7 day period = 53.3°C
  - MKT over 3 years would be 31.3°C (30°C storage for the rest of time)
  - 0.1% degradation over 7 days:
  - This amount of degradation would take 269 days at its proposed storage conditions (30°C) – therefore the excursion shortened the shelf-life by 262 days (9 months).
  - Shelf-life set at 5 years, but is projected to remain within specification (of 1.0%) for 7 years….

Humidity Excursions

In general, not a significant stability risk for packaged products.

Mainly because water permeation through packaging is slow relative to typical durations of humidity excursions

E.g. An elevated humidity excursion occurring over a 2 week period has a negligible effect on the humidity inside a HIS HDPE bottle containing 30 small tablets



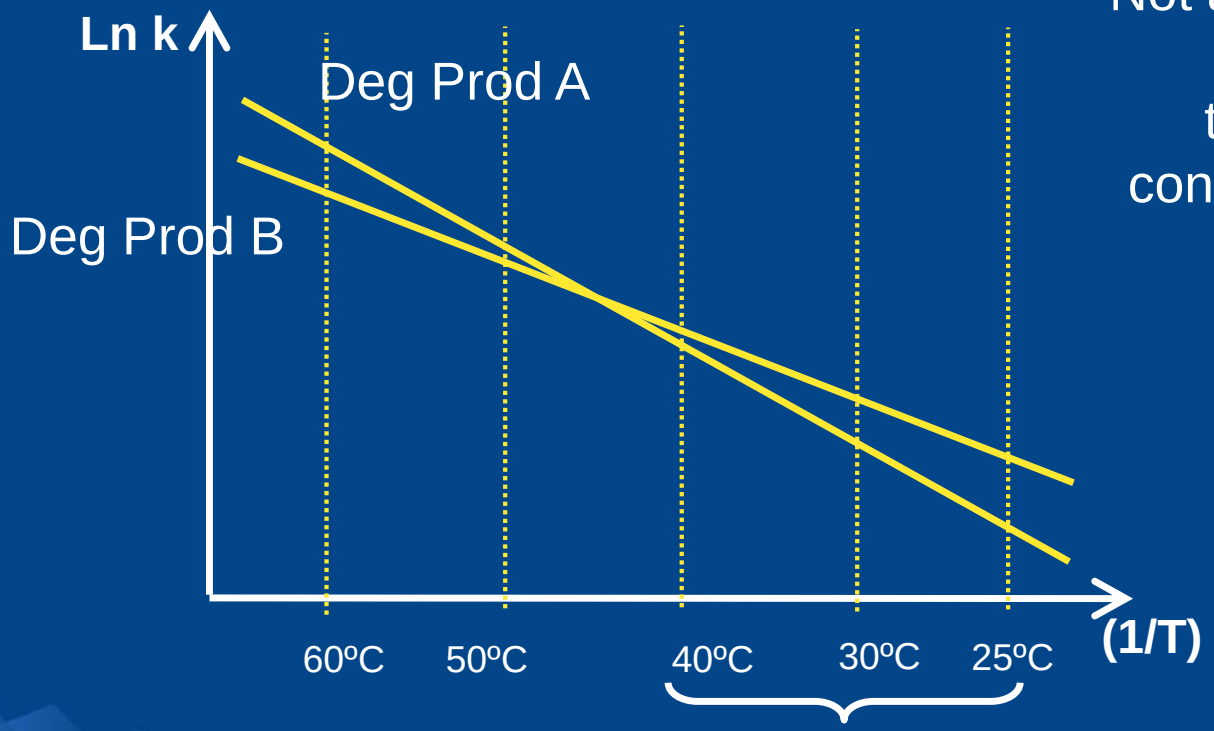
Formulation or Process Changes

- The same ASAP protocol (as discussed for temperature excursion) is also useful in formulation development and excipient compatibility studies:
  - Rapid (e.g. 2-3 wk)
  - Enables the effects of temperature and humidity to be modelled (so stability performance in any pack type and climatic zone can be predicted):

Package Type	Condition	Formn. A	Formn. B	Formn. C	Formn. D
30 count 60 cc HDPE Bottle	25ºC / 60% RH	2.8 years	10.3 months	2.5 years	14.4 months
30 count 60 cc HDPE Bottle + 1g Desiccant		4.6 years	14.8 months	3.5 years	23.8 months
PCTFE Aclar™ Ultrx 2000 Blister, 23.9 x 9.5 x 8.2 mm capsule		21.7 months	8.6 months	22.3 months	10.4 months
Foil/Foil cold-formed Blister, 23.9 x 9.5 x 8.2 mm capsule at		> 5 years	11.8 months	3.4 years	19.0 months
30 count 60 cc HDPE Bottle	30ºC / 65% RH	16.9 months	4.8 months	13.8 months	7.1 months
30count 60 cc HDPE Bottle + 1g desiccant		2.3 years	6.8 months	19.8 months	11.9 months
PCTFE Aclar™ Ultrx 2000 Blister, 23.9 x 9.5 x 8.2 mm capsule		10.7 months	4.1 months	10.3 months	5.2 months
Foil/Foil cold-formed Blister, 23.9 x 9.5 x 8.2 mm capsule		2.6 years	5.4 months	18.6 months	9.1 months

- But there can be a lot of samples to analyse / data to process if there are multiple formulations to assess or many different degradation products

Using a single accelerated condition to rank-order different formulations might provide misleading information



Not a problem with ASAP where multiple temperature / RH conditions are analysed

Formulation or Process Changes

- In early development, ASAP is typically run as a rapid screening tool
- In late-stage development, where greater accuracy may be required, it is generally a good idea to:
  - Use milder conditions
  - Have longer durations (decreasing temperatures by 10°C typically increases duration of protocol 4-fold)
  - Obtain multiple timepoints for each condition to enable a better assessment of the ‘fit-to-model’)

Summary

- Apologies for only briefly covering formulation and process changes, but I also discuss elements of this in my later presentation on the effects of drug load
- Obtaining stability data for unpackaged samples over a range of different temperatures and humidity conditions has a number of benefits and applications
- The effects of temperature and humidity can be modelled and extrapolated
  - Most products appear to conform to the same model
- Temperature excursions, formulation changes and process changes are just three applications

Thank You For Your Attention