PSE

APM

ADVANCED PROCESS MODELLING FORUM 2017
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Model-based methodology for accelerated stability studies of solid formulations

Edd Close – PSE Formulated Products Senior Consultant

gPROMS

Overview

- Introduction
- Background
- Workflow
- Applying the framework
- Future directions

Introduction

Context for the work presented in this presentation

- Exploratory work
  - Henrique Sardinha
  - make use of advanced gPROMS platform capabilities
    - parameter estimation – model calibration using data from accelerated tests
    - GSA – accounting for parameter uncertainty and variability in env. conditions
    - Optimisation
- Lay the foundations for a framework for future expansions
  - Development of more mechanistic (not first principles) models
    - account more explicitly for type of material
    - Implement models based on hypothesis from experts
    - use experimental data to discriminate between these models
- Initially we have considered a pharmaceutical industry perspective
    - We are moving forward with the understanding that the gPROMS platform capabilities and underlying framework are likely to have applications in other formulated product industries too

Background

Accelerated Stability Assessment Program Modelling

Product Stability – Product allowed storage time before any given degradation product compromises patient safety;

Typical stability program:
- 6 months of accelerated data under ICH conditions;
- At least 2 years of long term stability testing;

Chemical (in)stability
- Hydrolysis
- Photochemical reactions
- Reactions with excipients
- Oxidation

Physical (in)stability
- Deliquescence;
- Dissolution;
- Polymorphic changes;
- Disintegrant expansion;

Isoconversion –Time required for the heterogeneous solid state reaction to achieve a specification limit or degradant concentration, regardless of the extremely complex solid state-kinetics;

ASAP studies

-Accelerate degradation rates in order to test the stability of the formulation

Relative Humidity corrected Arrhenius Equation:

$$\ln(k) = \ln(A) - \frac{Ea}{R} \times \left(\frac{1}{T}\right) + B(RH)$$

Pseudo zero-order reactions can be considered due to the low conversion of solid dosage drugs into degradants (typically 0.5-1%)

The degradation rate (k) will be a combination of all the reactions occurring in the solid state.

Current situation in the pharmaceutical industry

Current stability programs

- Difficulty developing mechanistic understanding of stability processes
  - Sources of chemical/ physical instability
- High pressure to succeed at first time
  - High costs of stability programs

High uncertainty

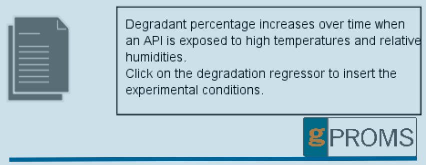
The **challenge:**

- Have a better understanding of the degradation experiments
- Ensure the new drug is stable enough to start an ICH stability program
- Determine the design space and **quantify** how external factors (temperature, relative humidity) and kinetic factors (Ea, Ln(A), B) contribute to drug instability

Workflow

Approach to the degradation assessment

1 Build **flowsheet model** of experiment



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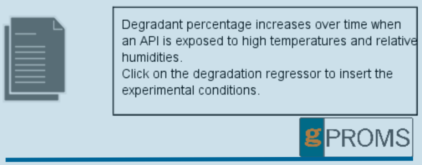

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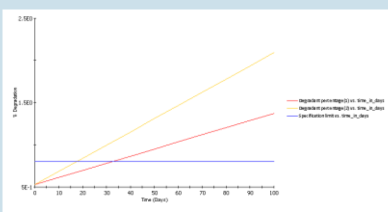

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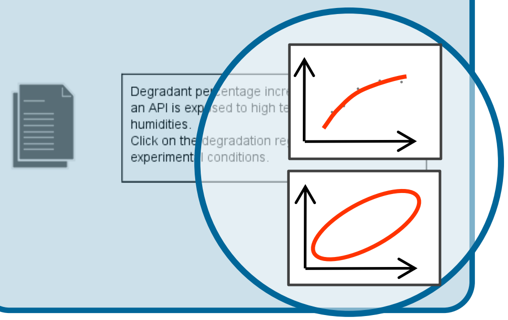

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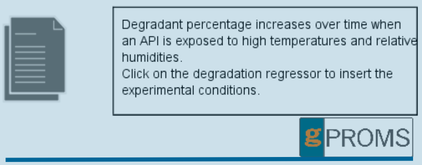

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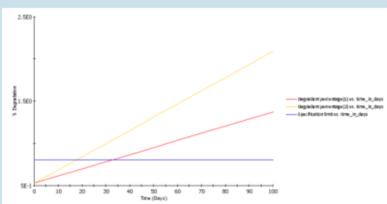

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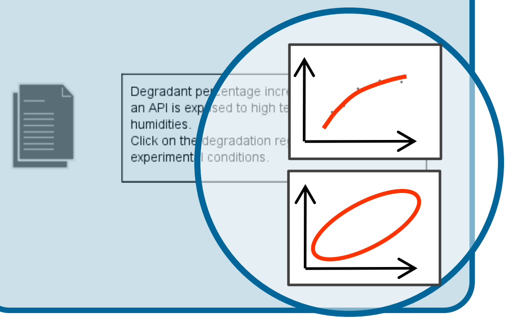

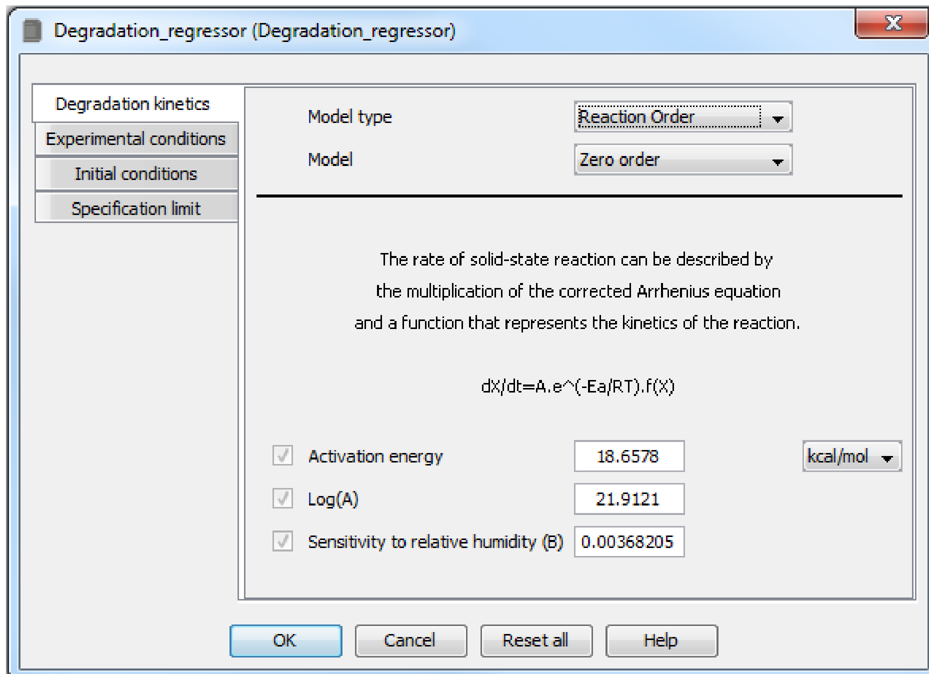

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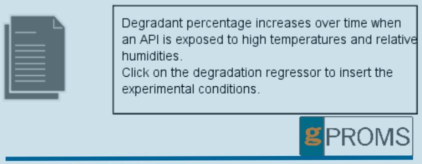

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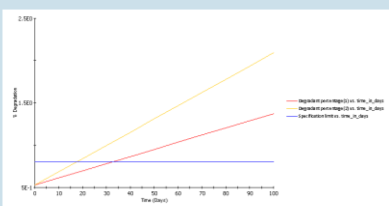

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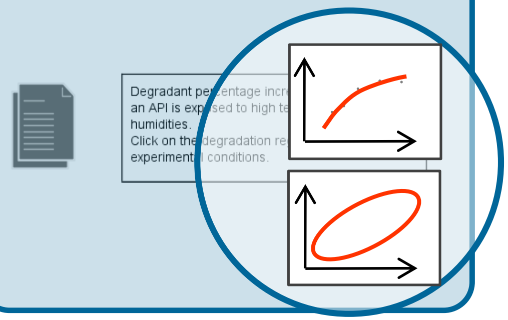

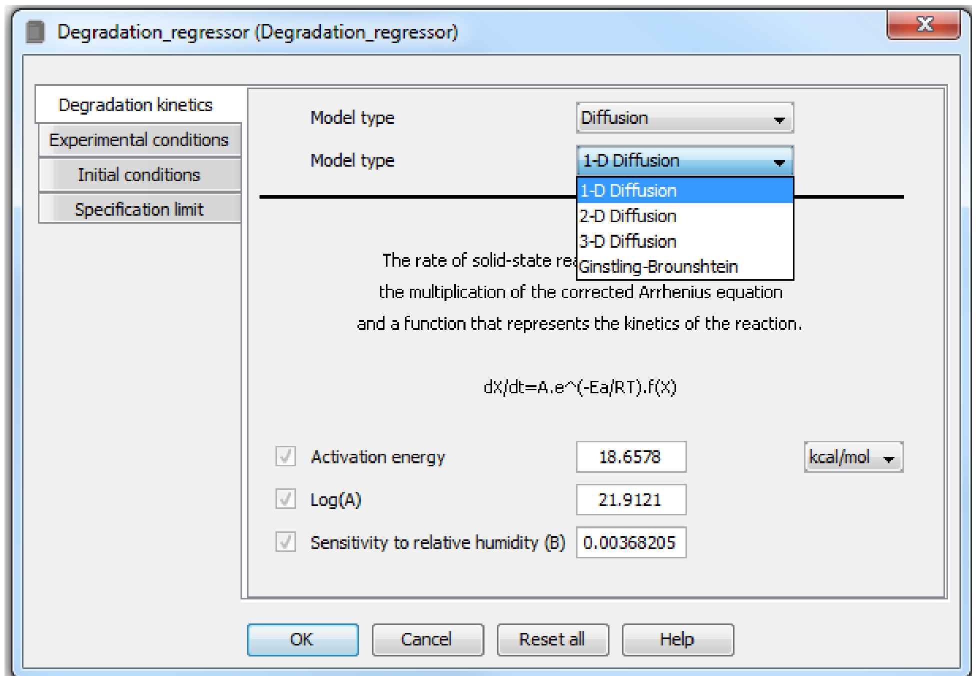

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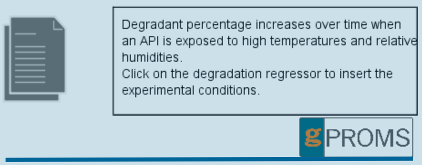

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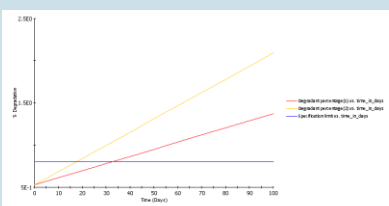

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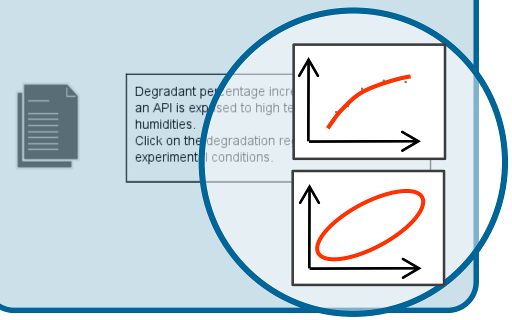

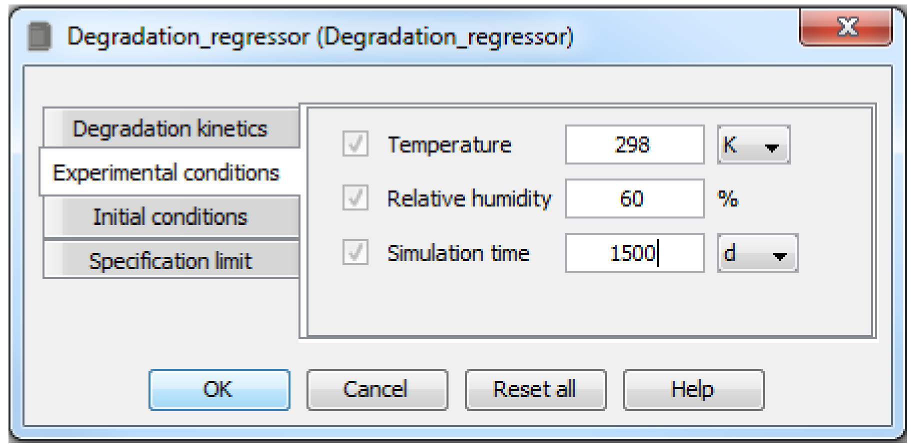

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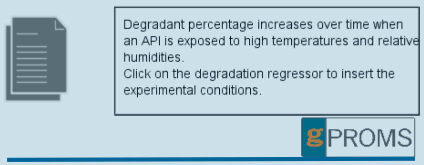

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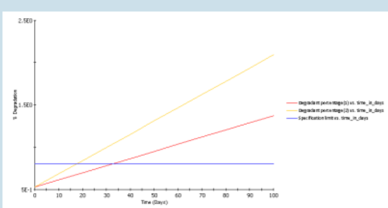

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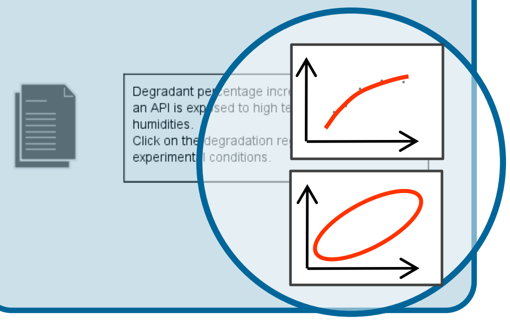

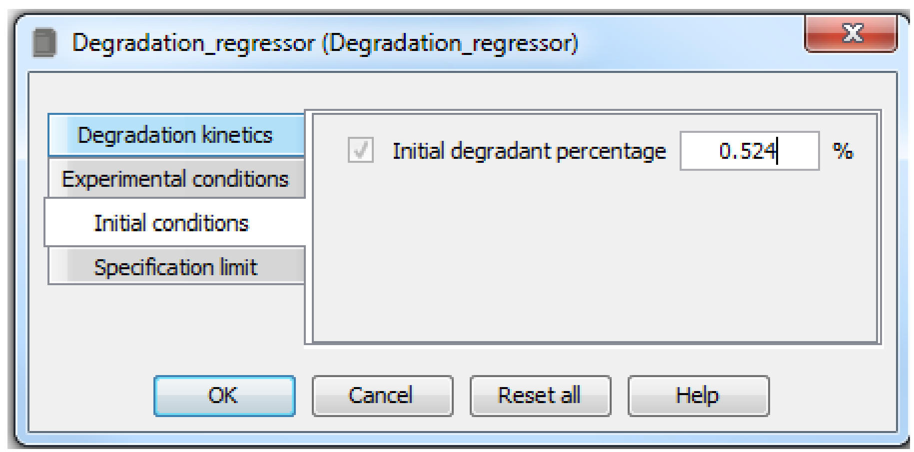

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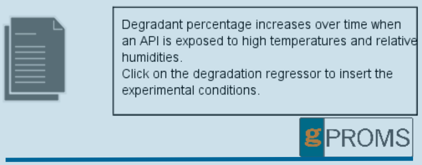

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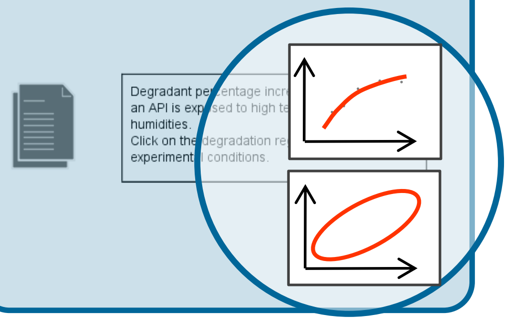

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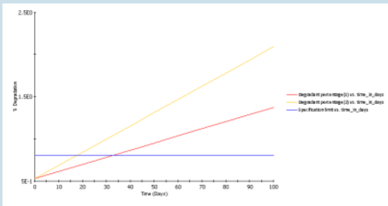

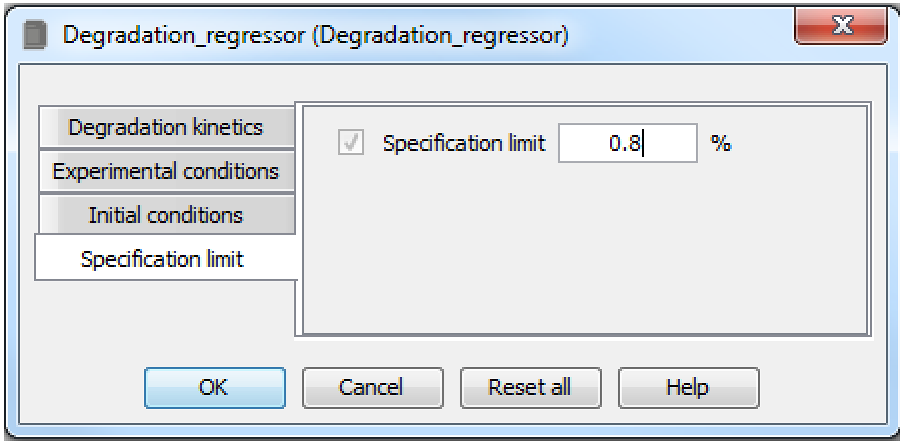

Approach to the degradation assessment

1 Build **flowsheet model** of experiment

Degradant percentage increases over time when an API is exposed to high temperatures and relative humidities.
Click on the degradation regressor to insert the experimental conditions.

gPROMS

Relative Humidity corrected Arrhenius Equation:

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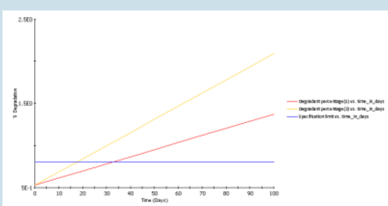

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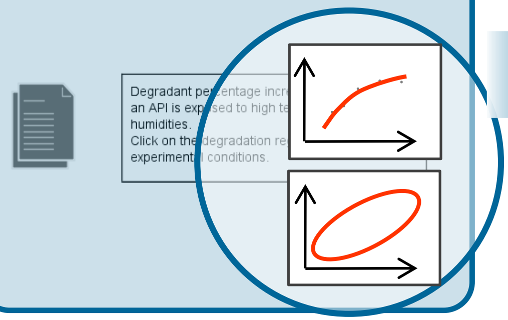
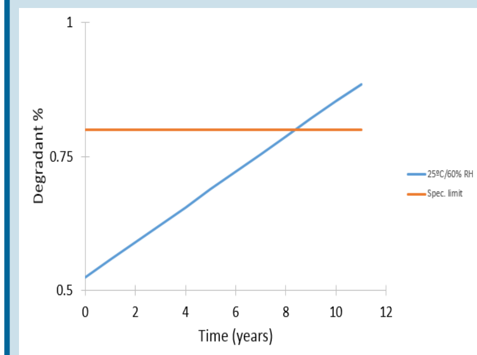
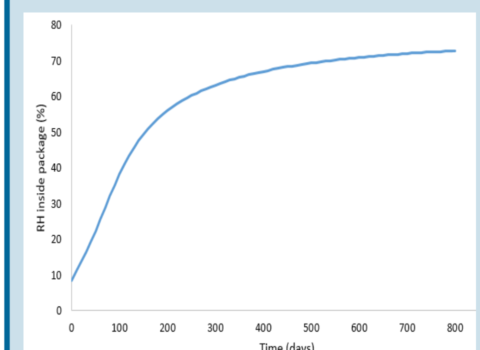


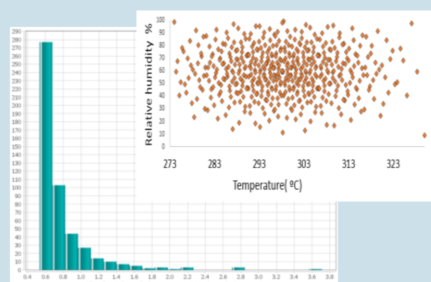
4 **Shelf-life analysis**



Packaging Integration



5 **Global Systems Analysis**



Applying the framework

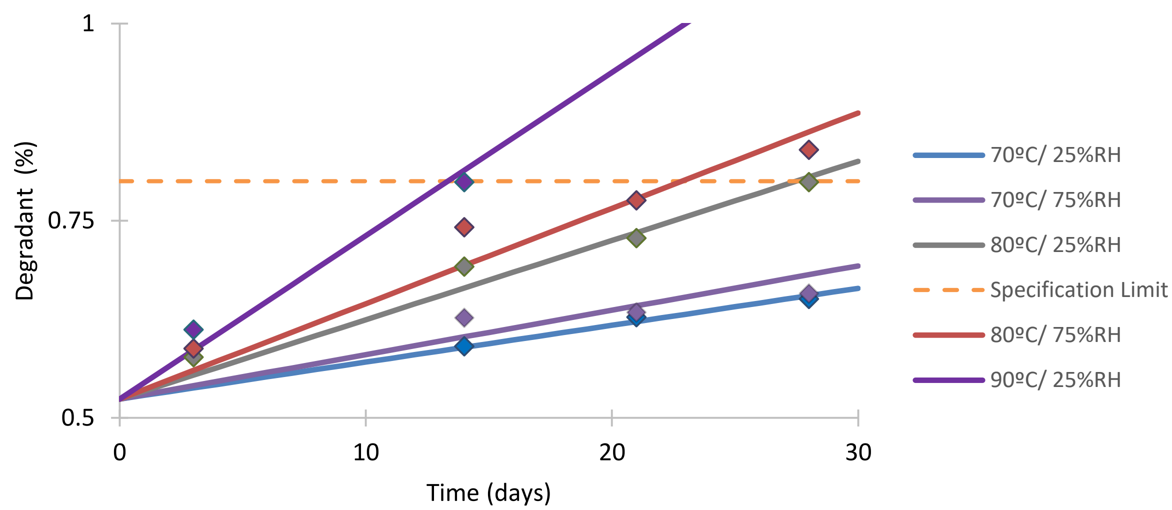
Execute experiments and estimate parameters

Applying the framework

1) Conducted experiments

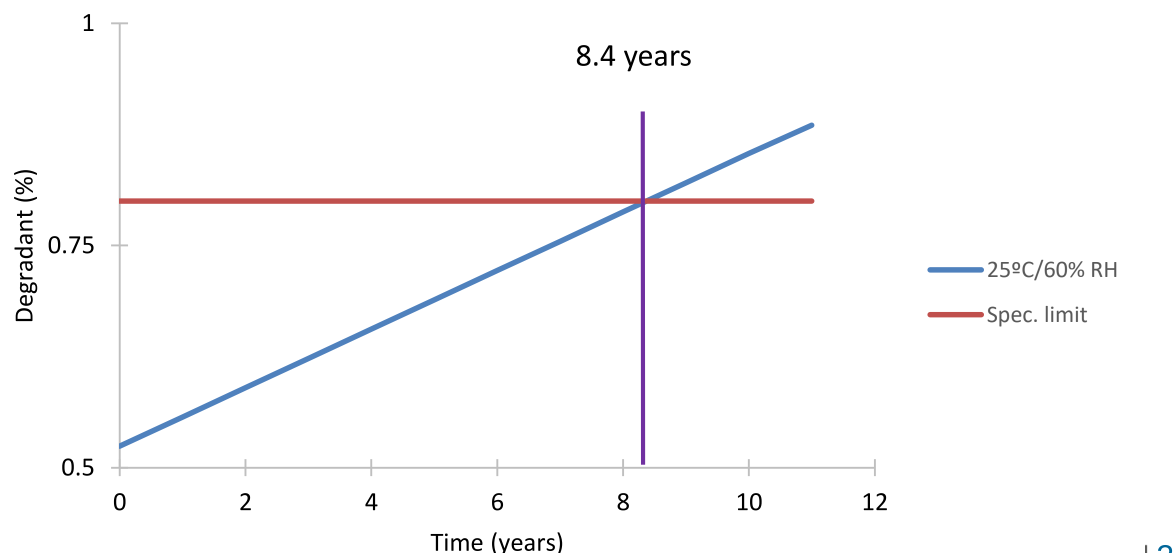
Sample degradation (%) over 30 days:

- 70ºC/ 25%RH
- 70ºC/ 75%RH
- 80ºC/ 25%RH
- 80ºC/ 75%RH
- 90ºC/ 25%RH

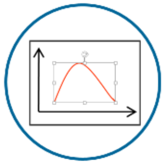


2) Parameter estimation

E_a= 18.4±1.97
Ln(A)= 21.54±2.77
B= 0.0037±0.0018



For the estimated parameters acquired at accelerated conditions, the model predicts a **shelf-life** of **8.4 years** at **25ºC/60%RH** for the tested API



Normal Distribution

Why?
To explore variable environmental conditions to which the sample might be exposed

What?
Monte Carlo uncertainty analysis on **500 random samples (Sobol sampling)** of the 2 main factors:
- **Temperature**
- **Relative humidity**

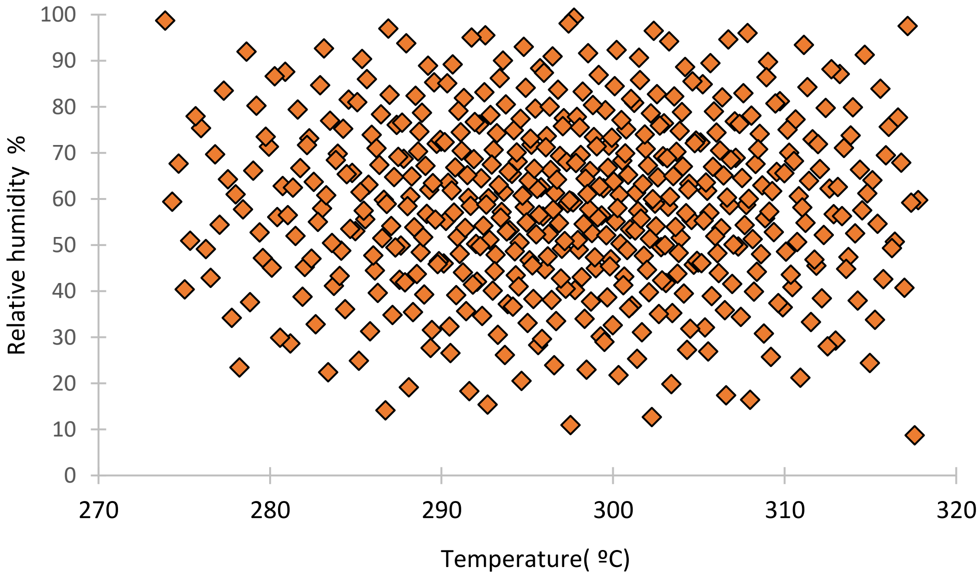
When?
2 year shelf-life (standard targeted shelf life for pharmaceutical drugs)

Response:
- **Degradation percentage**

```
Global system analysis took 4 seconds.
Total CPU time: 0.905s (64% system time)
```

Temperature:
- Mean= 298K
- STD= 12K

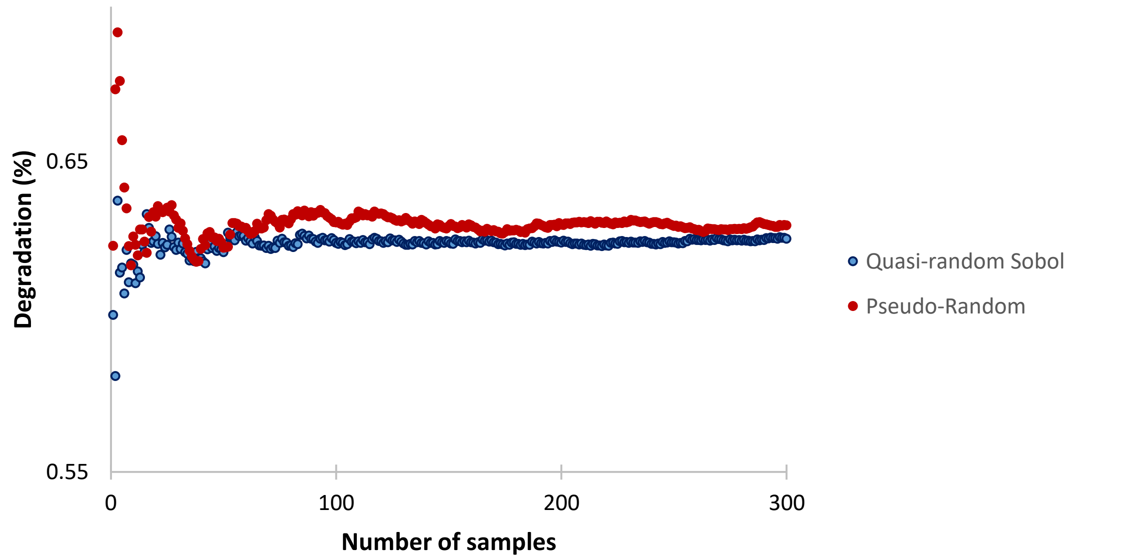
Relative humidity:
- Mean=60%
- STD=20%



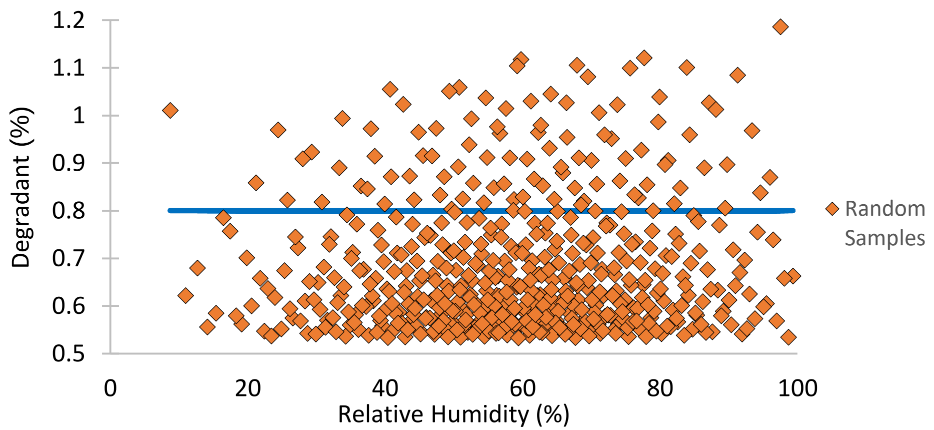
Shelf life analysis - Environmental variability

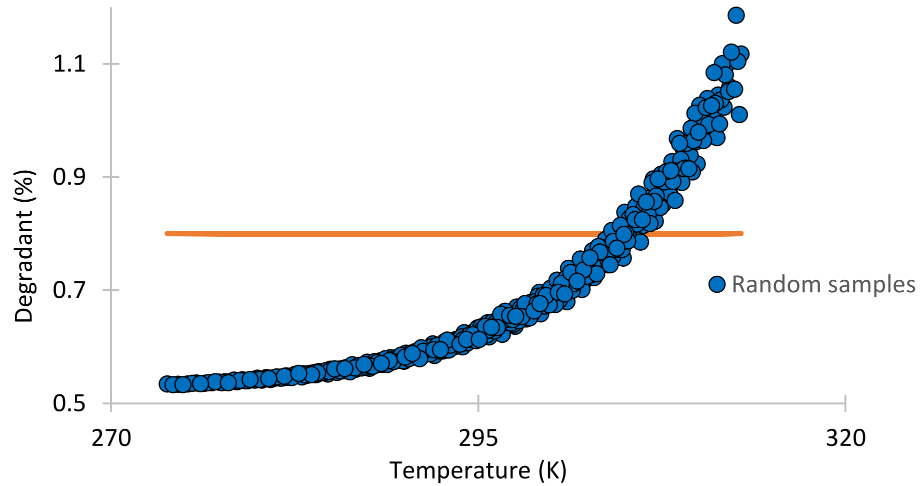
Applying the framework

Why 500 samples with quasi-random Sobol sampling?



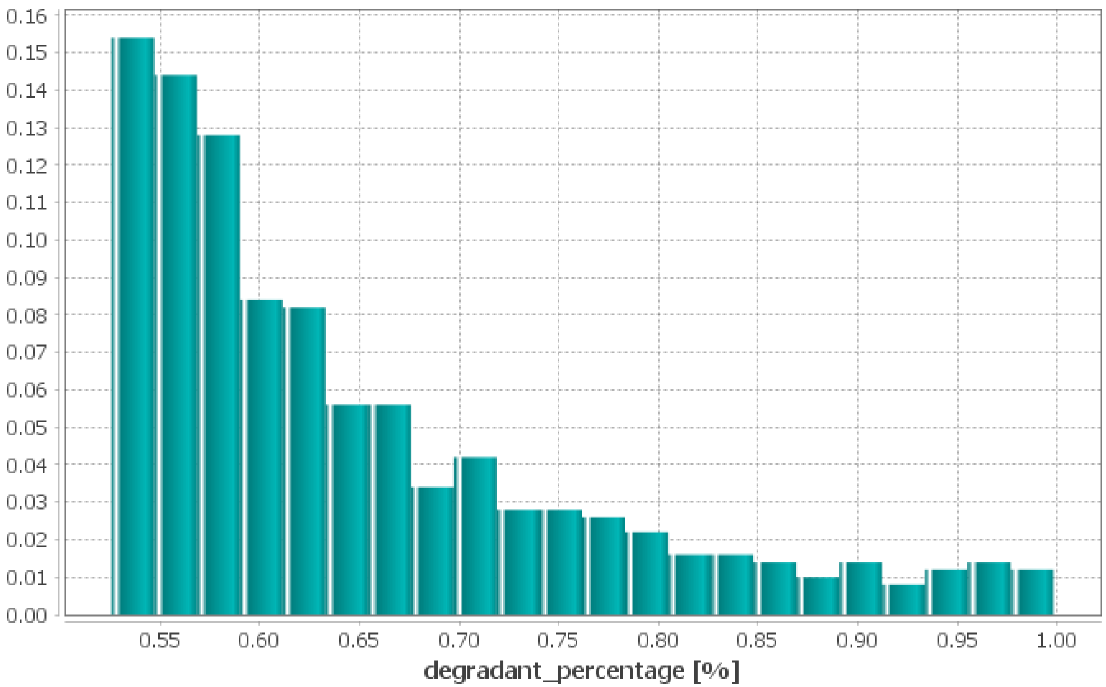
Analysis performed on the 2th year of shelf-life





Shelf life analysis - Environmental variability

Applying the framework



Degradation %	
Expected value	0.647
STD	0.114
Minimum	0.525
Maximum	0.998

Statistical analysis target after 2 years of the suggested shelf-life:

- **12.4%** of all samples **are already over the spec. limit** of 0.8% degradant
- A significant number of samples will soon be over the specification limit

Incorporating uncertainty is vital in order to draw valid conclusions, and should become an integral part of modelling workflows in the future

Shelf life analysis – Parameter uncertainty

Applying the framework

Normal distribution

Temperature:

- Mean= 298K
- STD= 12K

Relative humidity:

- Mean=60%
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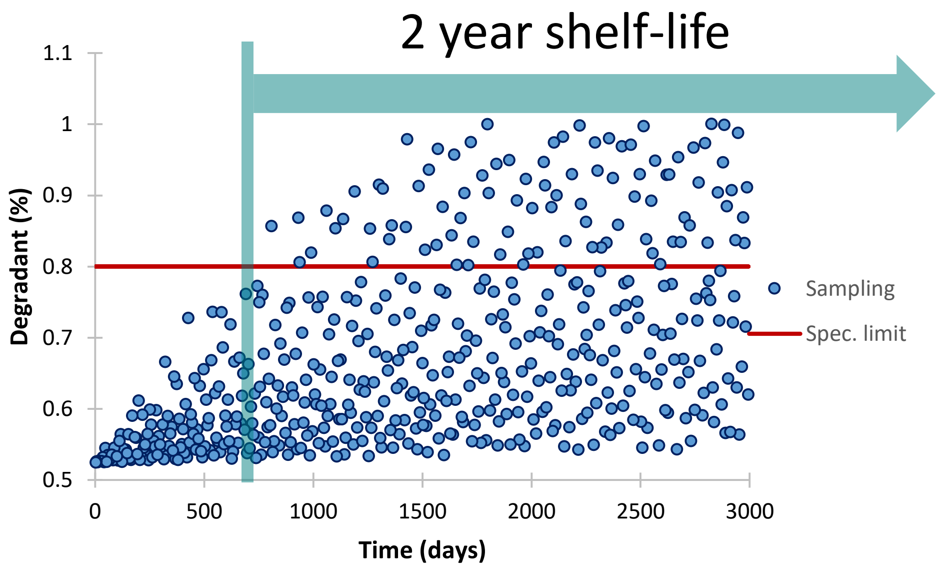


100 000 samples

P(failing spec)=12.4%

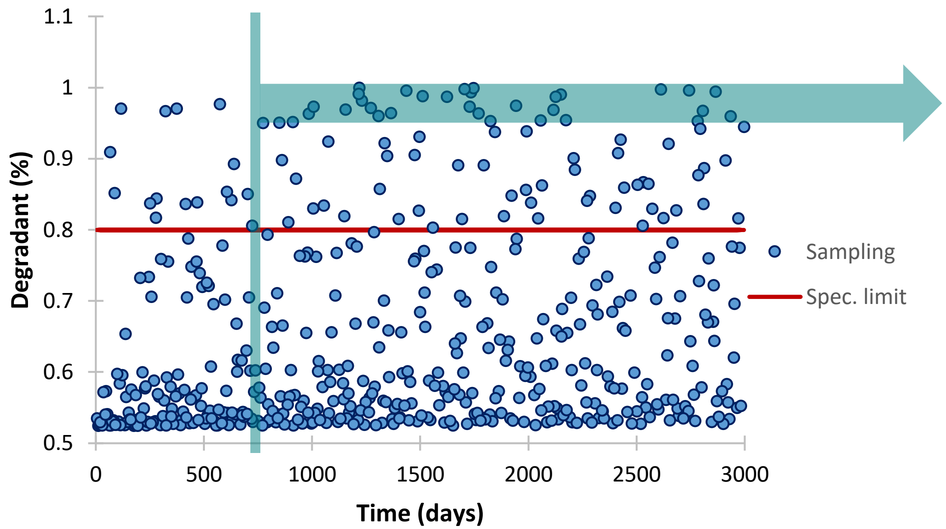
Uniform distribution on kinetic parameters

16.73<**Ea**<20.59

19.18<**Ln(A)**<24.64

0.0018<**B**<0.0055

95% confidence intervals



100 000 samples

P(failing spec)=35.8%

Shelf life analysis – Factor sensitivity

Applying the framework

Temperature is the key driver in the response space amongst the external parameters

	Degradation (%)	
	1st Order	Total effect
RH	0.00397	0.00662
T	0.9935	0.99571

Activation energy is the key driver in the response space amongst the kinetic parameters

	Degradation (%)	
	1st Order	Total effect
Ea	0.6117	0.7630
Ln(A)	0.4731	0.6262
B	0.00166	0.00300

Future directions

Future directions
not mutually exclusive

- Recreate ASAP functionality within gFP environment
  - very basic model
  - make use of advanced gPROMS platform capabilities
    - parameter estimation – model calibration using data from accelerated tests
    - GSA – accounting for parameter uncertainty and variability in env. conditions
    - optimisation
- Development of more mechanistic (not first principles) models
  - account more explicitly for type of dosage form
  - implement models based on hypotheses from experts within alliance
  - use experimental data to discriminate between these model
- Connectivity with manufacturing models – sensitivity of stability with respect to manufacturing decisions and disturbances

Thank you