Predictive Stability at AstraZeneca – Strategy, Case Studies & more…

Alexander Abbott

Associate Director

Oral Product Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK.

Dr Carolyn Gordon

Senior Director & Group Manager

CMC Regulatory Affairs, Global Regulatory Science & Strategy, Oncology R&D, AstraZeneca, Macclesfield, UK.

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Science of Stability 2022 – The Science Institute, Philadelphia, PA, USA

Agenda

1 Introduction: ICH Q1/Q5C update

2 Predictive Stability Strategy at AstraZeneca

3 Recent Developments & Routine Application

4 Case Studies – Across the Stages of Development
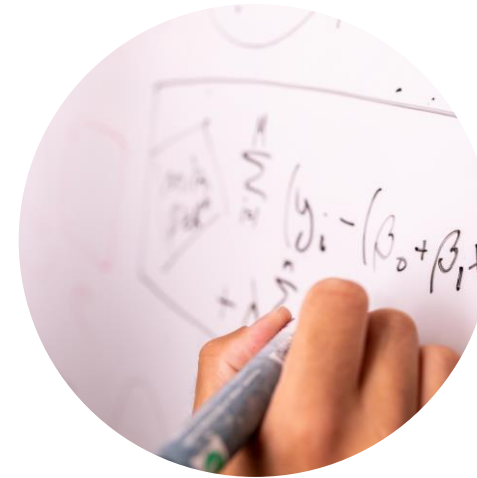
5 External Activities

Aims of this Presentation

Communicate AstraZeneca's vision in this area.

Invite collaboration; technical, strategic, regulatory, academic.

Share some of our science.

Promote awareness of ICH update.

ICH Stability Guidance Revision

Initial proposal for new topic (EFPIA, Global Self-Care Federation, Heath Canada, Canada, IGBA, JPMA, MFDS, Republic of Korea, and PhRMA with support of the ICH Quality Discussion Group (QDG))**:**

'Ambiguities of the ICH Stability concept: To resolve this patchwork [ie. multiple separate guidelines], most of the content of the existing guidelines ICH Q1A-E, ICH Q5C and potentially the content of the withdrawn Q1F and WHO's Stability guideline can be transferred into one combined ICH Q1 guideline with integrated addenda/annexes being clear per topic. This allows for a) Removing these ambiguities and uncertainties (e.g., related to the interpretation and application of these guidelines) and b) Harmonizing the stability regime and implementation for both small molecules (chemical entities) and biotech/biological products in the respective API [drug substance] or drug product stage. Furthermore, **the capacity to model stability data using modern principles to predict the [re-test period / shelf-life] is another development that makes targeted revisions of ICH Q1 series critical** as it will potentially enable earlier patient access to safe, effective and high-quality medicines.'

Topic endorsed at ICH Virtual Assembly, June 2021
Informal Working Group (IWG) initiated August 2022
Topic on agenda at F2F ICH Assembly, November 2022; IWG will also meet
Expert Working Group (EWG) initiation will follow, with target timelines (date tbd)

Issues highlighted in the ICH QDG proposal

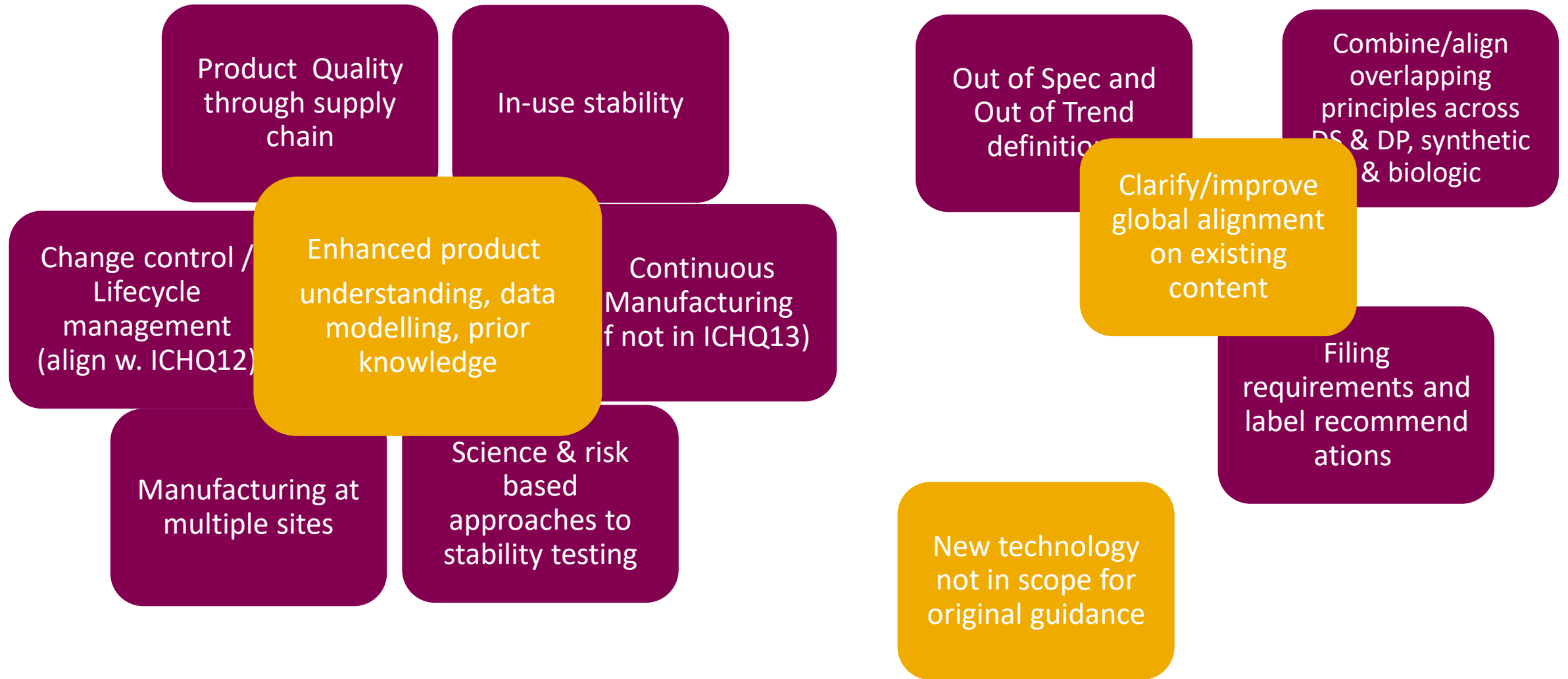|			
Enhanced product understanding, data modelling & prior knowledge*	In-use stability	Combine/align overlapping principles across DS & DP, synthetic & biologic	Science & risk based approaches to stability testing
Change control / Lifecycle management (align w. ICHQ12)	Continuous Manufacturing (if not in ICHQ13)	Product Quality through supply chain	Out of Spec and Out of Trend definitions
Manufacturing at multiple sites	New technology not in scope for original guidance	Clarify/improve global alignment on existing content	Filing requirements and label recommendations

* Includes e.g., modelling techniques and selections of batches, application of an holistic, science and risk based approach to stability, allowing for the justification of appropriate studies to determine shelf life and retest date; New technologies and techniques such as the use of accelerated kinetics based stability models; Advances in understanding and prior knowledge for biological drugs supporting extrapolation; Harmonisation of expectations for lifecycle changes (which will be more prevalent where products are rapidly developed for an unmet medical need)

Issues highlighted in the ICH QDG proposal

Product Quality through supply chain

In-use stability

Out of Spec and Out of Trend definition

Combine/align overlapping principles across DS & DP, synthetic & biologic

Change control / Lifecycle management (align w. ICHQ12)

Enhanced product understanding, data modelling, prior knowledge

Continuous Manufacturing (if not in ICHQ13)

Clarify/improve global alignment on existing content

Manufacturing at multiple sites

Science & risk based approaches to stability testing

Filing requirements and label recommendations

New technology not in scope for original guidance

Science & Risk Based Stability: Industry Drivers

Clinical

- Develop robust products earlier

- Shorter time to clinic/patient

- Clinical supply chain management (match supply to demand, optimum shelf life)

- Increased understanding of degradation mechanisms compared to traditional stability studies, which primarily seek to confirm stability

- Support accelerated development, especially for breakthrough indications

- 'Stability by design' : commercial product/ pack that maximises eventual shelf life

- Facilitate post approval change management

Aim: maximise quality, minimise wasted time and resource

Commercial

Predictive Stability Strategy at AstraZeneca

- Dedicated activity in 2021 to map out predictive stability capability build at AstraZeneca.

- Alignment with key business goals;

  Reduction in development to launch time.

  Implementation of breakthrough technologies.

  Achieve zero carbon emissions from our operations.

  Contribution to financial targets.

- Enabled by application of predictive stability on all <u>applicable</u> projects.

Predictive Stability Strategy at AstraZeneca

A leading Predictive Stability capability which delivers substantial and sustainable benefits to AZ projects

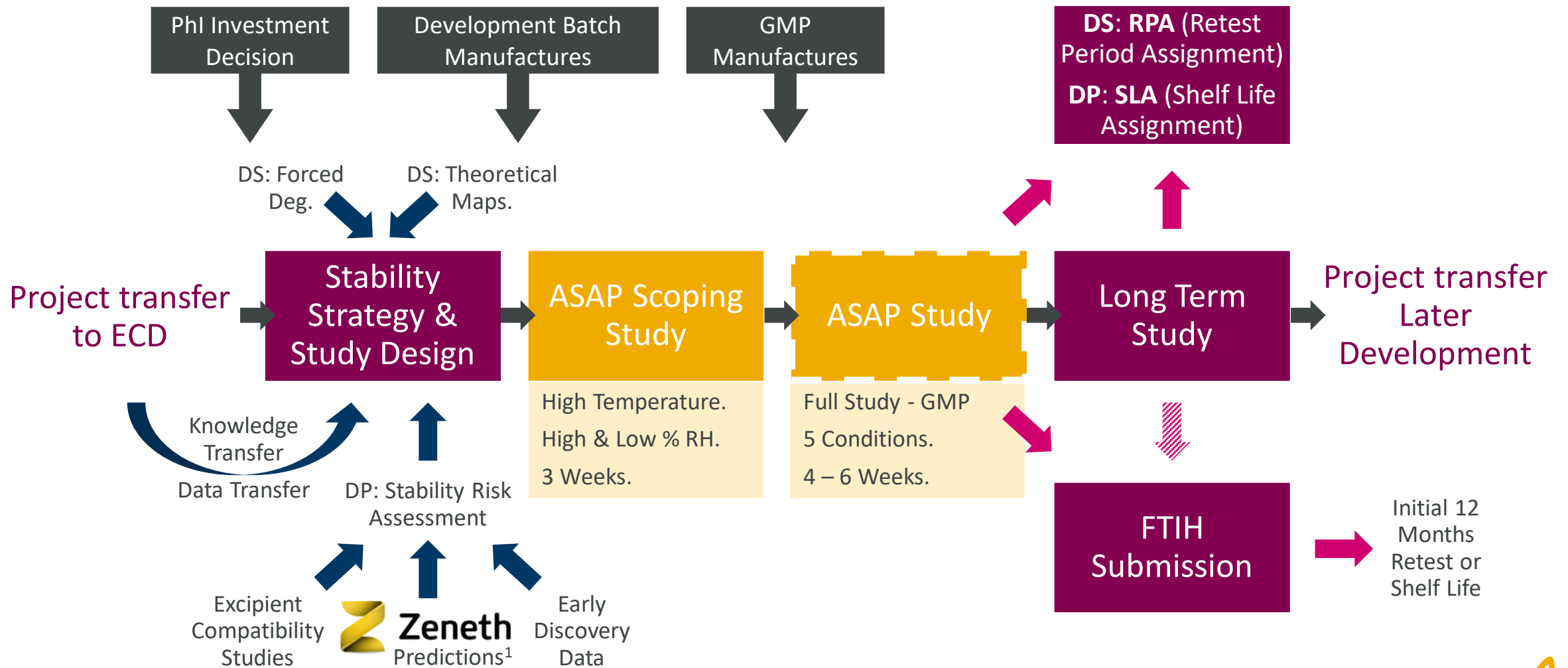| Project Delivery	External Impact	People, Processes & Capability	Technology Strategy
Predictive stability is a routine approach used across the development and on-market portfolio for a range of applications including reduction in project lead time	AstraZeneca is a key contributor to technical progress and external advocacy in the area of predictive stability	A cross-functional team with multiple experts across the business exists as the core capability for running predictive stability studies.	A robust and forward facing technology strategy enables the delivery of quality predictive stability work packages.

Recent Developments

- Purchasing of new **GMP climate chambers** at UK development site.

- Equivalent set up in another development site.

- Opportunities for **automation** to help handle the high sample volume generated by predictive stability studies.

- Growing list of **contract research organisation** (CRO) partners for predictive stability.

Predictive Stability Routinely Applied in Early Clinical Development

PhI Investment Decision

Development Batch Manufactures

GMP Manufactures

DS: Forced Deg.

DS: Theoretical Maps.

DS: **RPA** (Retest Period Assignment)
DP: **SLA** (Shelf Life Assignment)

Project transfer to ECD

Stability Strategy & Study Design

ASAP Scoping Study

ASAP Study

Long Term Study

Project transfer Later Development

Knowledge Transfer

Data Transfer

DP: Stability Risk Assessment

High Temperature.
High & Low % RH.
3 Weeks.

Full Study - GMP
5 Conditions.
4 – 6 Weeks.

FTIH Submission

Initial 12 Months Retest or Shelf Life

Excipient Compatibility Studies

Zeneth Predictions[1]

Early Discovery Data

Case Studies Across the Stages of Development

Case Study 1: Derisking a Post-Approval Change

Case Study 1: Derisking a Post-Approval Change
Background & Protocol

- A second supplier for a **functional excipient** was required for an on-market small molecule OSD product.

- Several potential second suppliers had been investigated previously, ruled out for various reasons.

- Excipient serves as a formulation stabilizer, limiting formation of **Degradant 1**.

- **Aim**: De-risk the large-scale manufacture, process validation and stability set down.

- Description, Tablet Weight, **Degradation Products** & XRPD were investigated.

- Study duration: **42 days**.

- Study conditions: **50 – 80°C**, **11 – 75% RH**.

Case Study 1: Derisking a Post-Approval Change
Degradant 1– Experimental Data
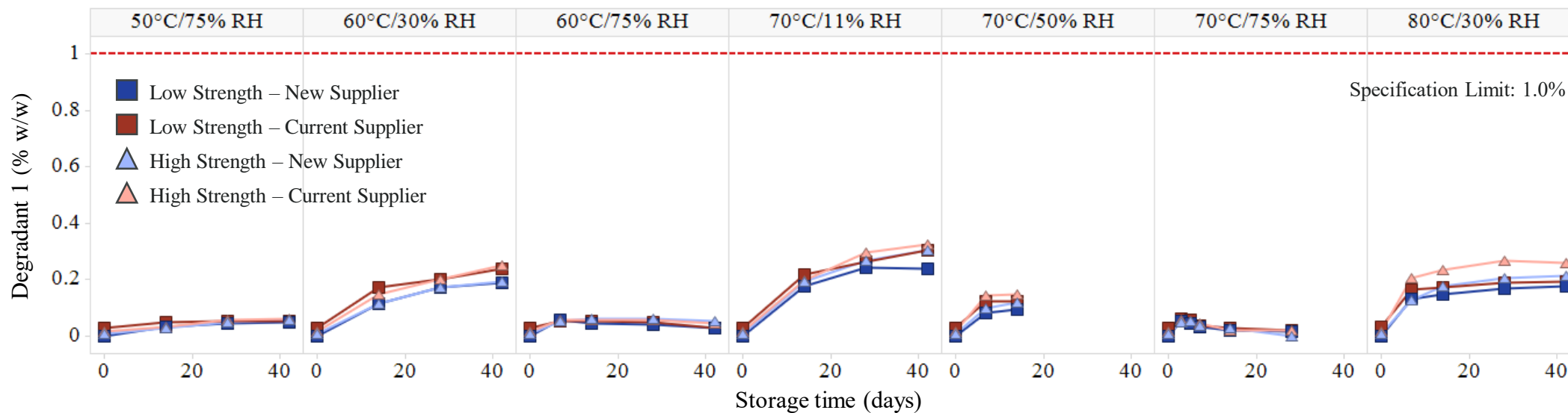
- Data suggests that the functional excipient successfully inhibits the formation of **Degradant 1**.

- The data are too far from the specification limit for standard ASAP modelling.

- **Conclusion**: Not shelf-life limiting, excipient **supplier is a viable choice**.

Case Study 1: Derisking a Post-Approval Change
Degradant 2 – Experimental Data

- Data suggests formation of **Degradant 2** is very similar for formulations with each supplier for a given strength.

- Isoconversion is reached for some conditions, extrapolation required at others.

- Only **low strength** chosen for modelling – high strength more stable, all conditions.

Data has been curtailed to include only those points up to approximately 2x the specification limit to avoid including excessive degradation in downstream modelling.
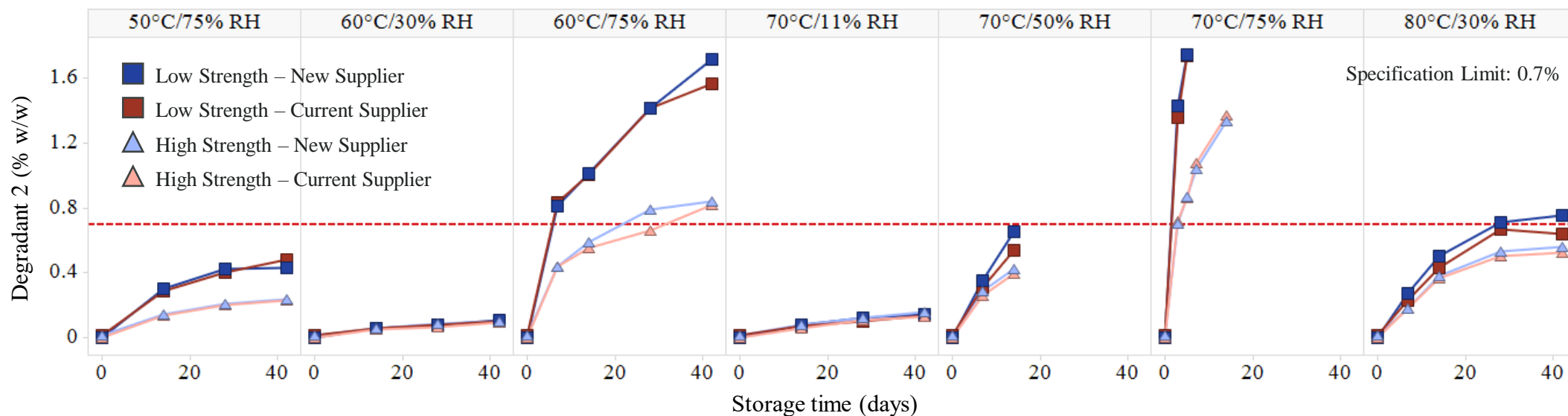
Case Study 1: Derisking a Post-Approval Change

Degradant 2 – Stability Modelling[2]

Example (■ Low Strength – Current Supplier)

1. Model quality indicators are good.

2. Model fit is reasonable for the data.

3. Some significant extrapolation required at certain conditions.

4. Minimal residual error in the modelling.

1

lnA	35.3
E_a	29.1 kcal/mol
B	0.0755
R^2	1.00
Q^2	1.00

2

4
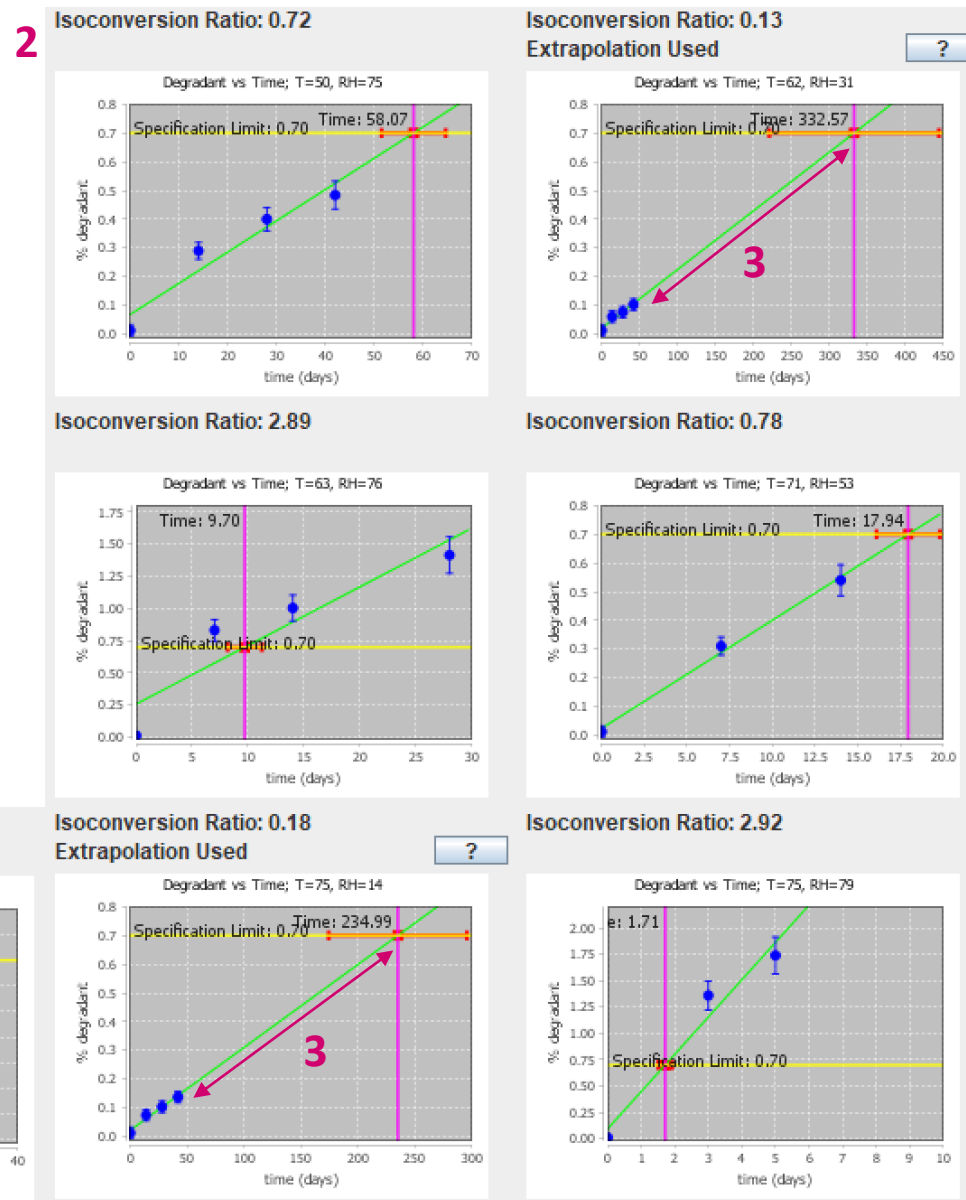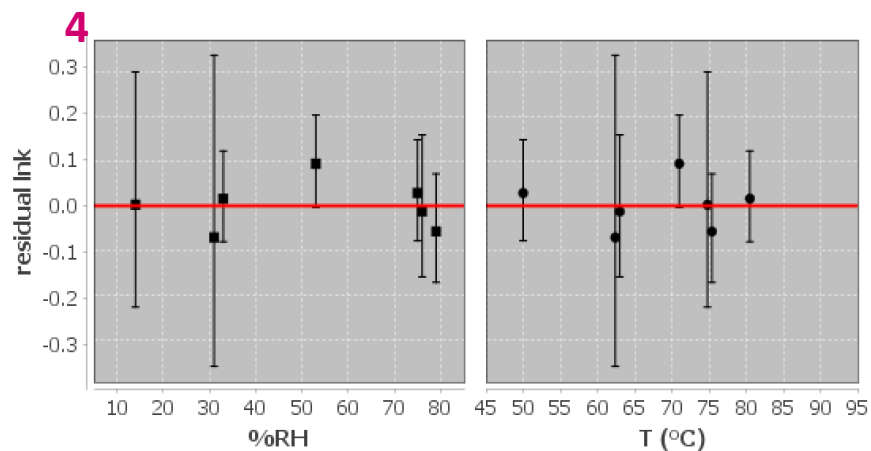
# Case Study 1: Derisking a Post-Approval Change
Conclusions

- Able to suggest stability behaviour for the low strength material at various long term stability conditions and conclude that the two batches are equivalent for stability.

- **Impact**: Reduce the risk of scale up manufacture & stability set down.

- In future, aim for this style of approach to be sufficient to justify a post-approval change.
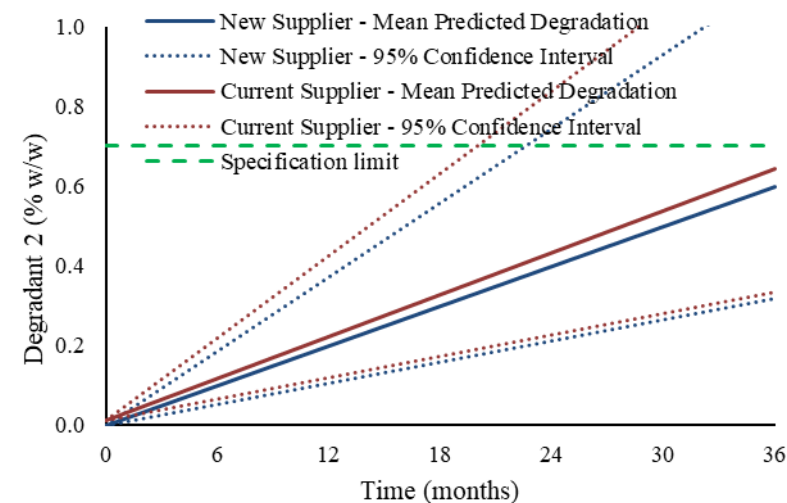
Software used: ASAPprime v6.0.1 (FreeThink Technologies Inc., CT, USA).
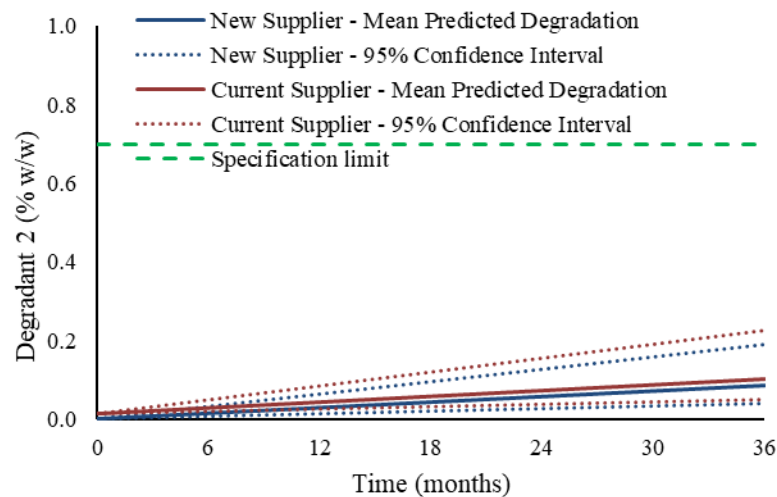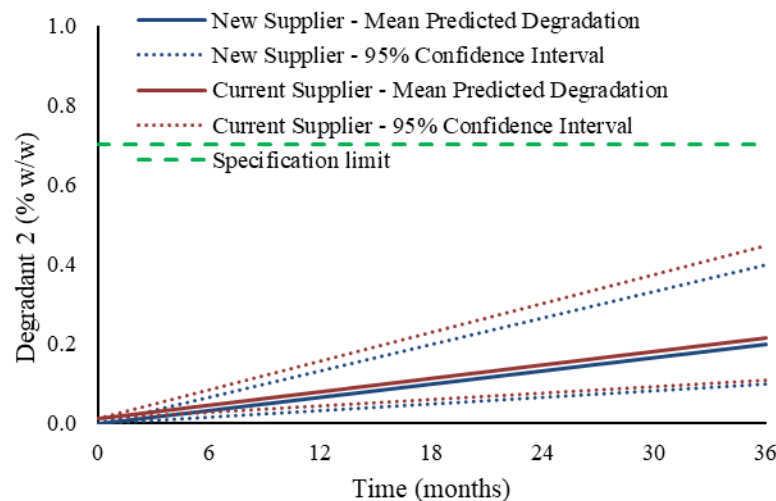
Case Study 2: Understanding N-Nitrosamine Formation

Case Study 2: Understanding N-Nitrosamine Formation
Background & Protocol

- N-nitrosamines are potential carcinogens which have been identified in pharmaceuticals across the industry.

- Requirement of a vulnerable amine (e.g. the API, or an impurity) and a nitrosating agent (e.g. API, packaging, excipient)[3].

- Analytical challenges associated with quantifying at ppb levels for small nitrosamines.

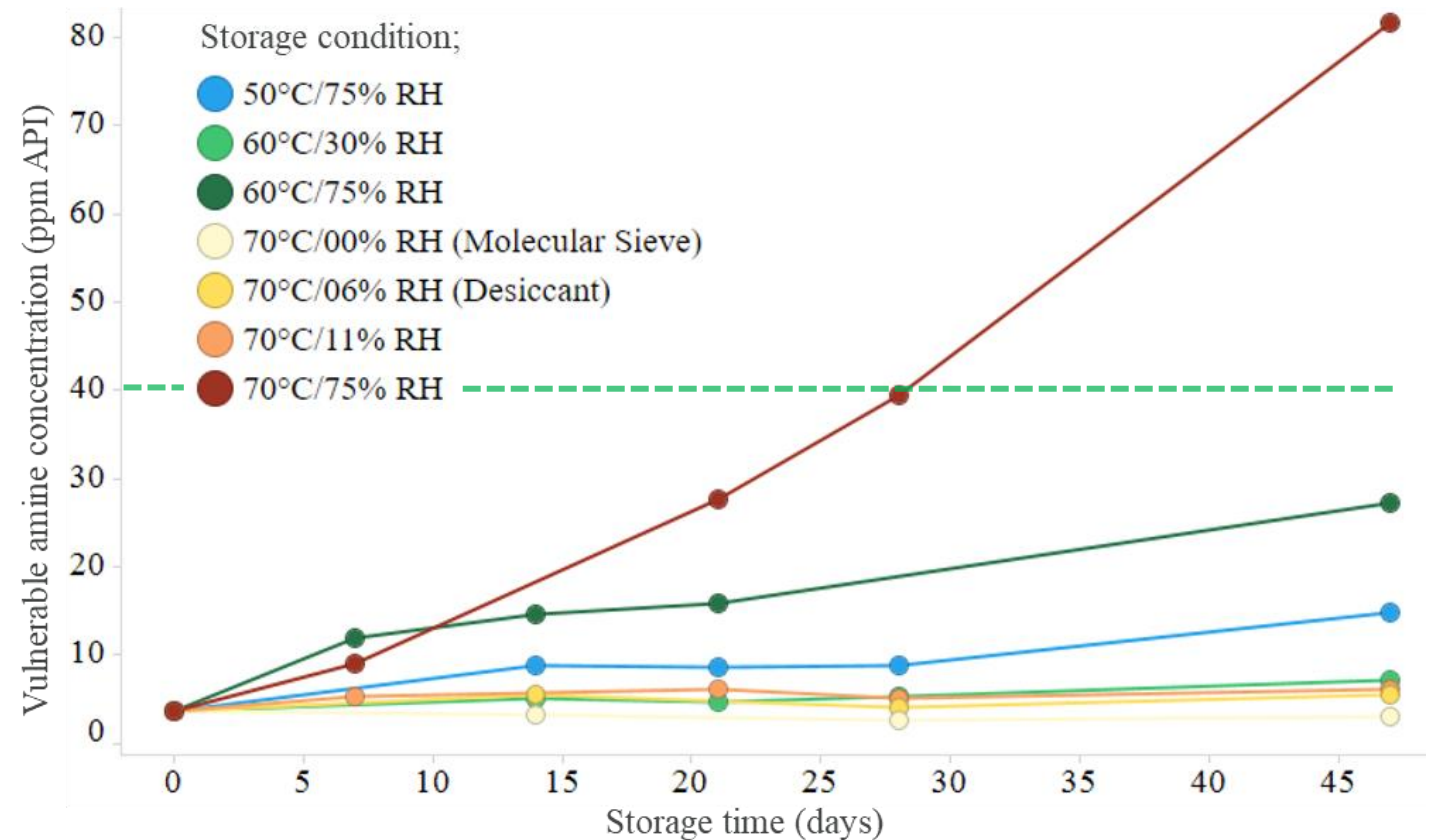- Investigated both the nitrosamine & the vulnerable amine precursor.

- Study duration: **47 days**.

- Study conditions: **50 – 70°C, 11 – 75% RH** & conditions using desiccant & molecular sieves.

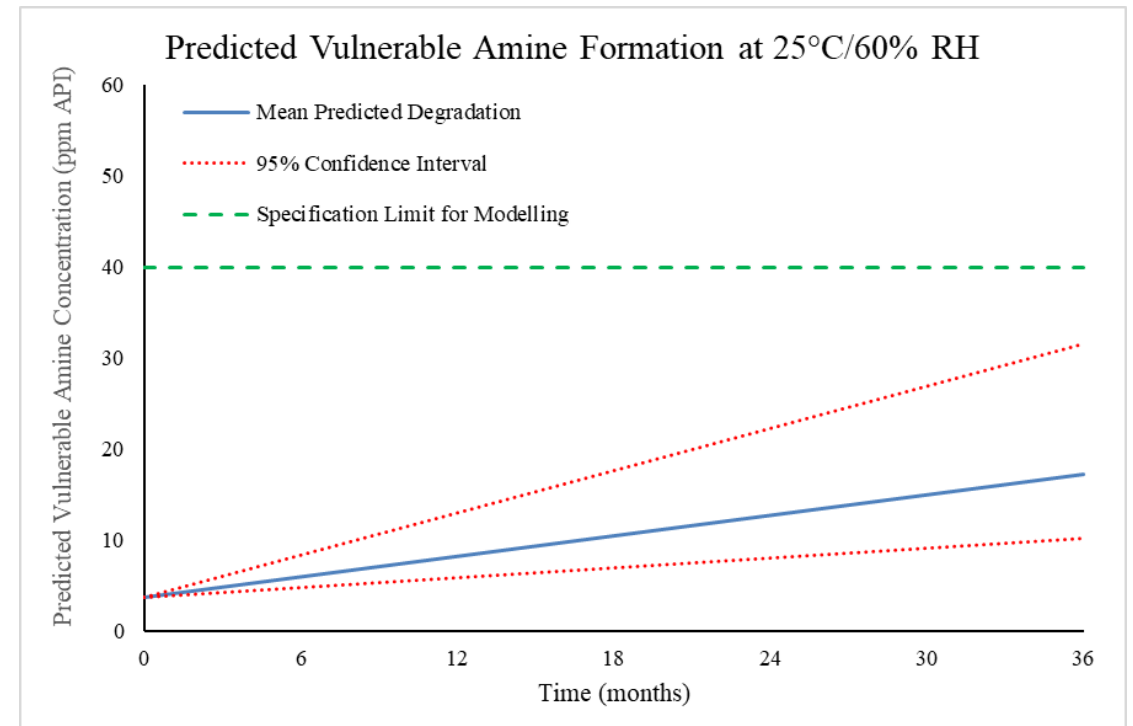# Case Study 2: Understanding N-Nitrosamine Formation
Experimental Data

- N-nitrosamine itself showed poor trending, high variability vs. change observed.

- Vulnerable amine precursor did trend well at low ppm levels.

- Clear relationship with **T & % RH**.

- Evidence that the packaging (desiccant) inhibits formation.

- Arbitrary limit of **40 ppm** API was used for modelling. Some conditions have very low degradation, so extrapolation is high.

Storage condition:
- 50°C/75% RH
- 60°C/30% RH
- 60°C/75% RH
- 70°C/00% RH (Molecular Sieve)
- 70°C/06% RH (Desiccant)
- 70°C/11% RH
- 70°C/75% RH

Two data points removed due to a suspected laboratory error, mix up of 2 samples.

Case Study 2: Understanding N-Nitrosamine Formation

Modelling & Prediction[2]

- The results were modelled using an ASAP approach and used to generate a prediction at a common stability study condition.

- The modelling would benefit from optimization in future studies, higher % RH.

- This was used to inform the project of the **indirect** potential of nitrosamine formation in the drug product over the shelf-life.

- Reassurance over current pack configuration.

- Formed part of the output from a practical problem solving (PPS) exercise.

Predicted Vulnerable Amine Formation at 25°C/60% RH

- Mean Predicted Degradation
- 95% Confidence Interval
- Specification Limit for Modelling

Case Study 3:
Justification of
Specifications for DP

Case Study 3: Justification of Specifications for DP
Background & Protocol

- Extensive predictive stability support for an accelerated project.

- Stability likely to be critical path for marketing application.

- Some moisture sensitivity shown during development & early stability studies.

- Predictive Stability applied to investigate the potential for elevated water content at time of commercial drug product packing.

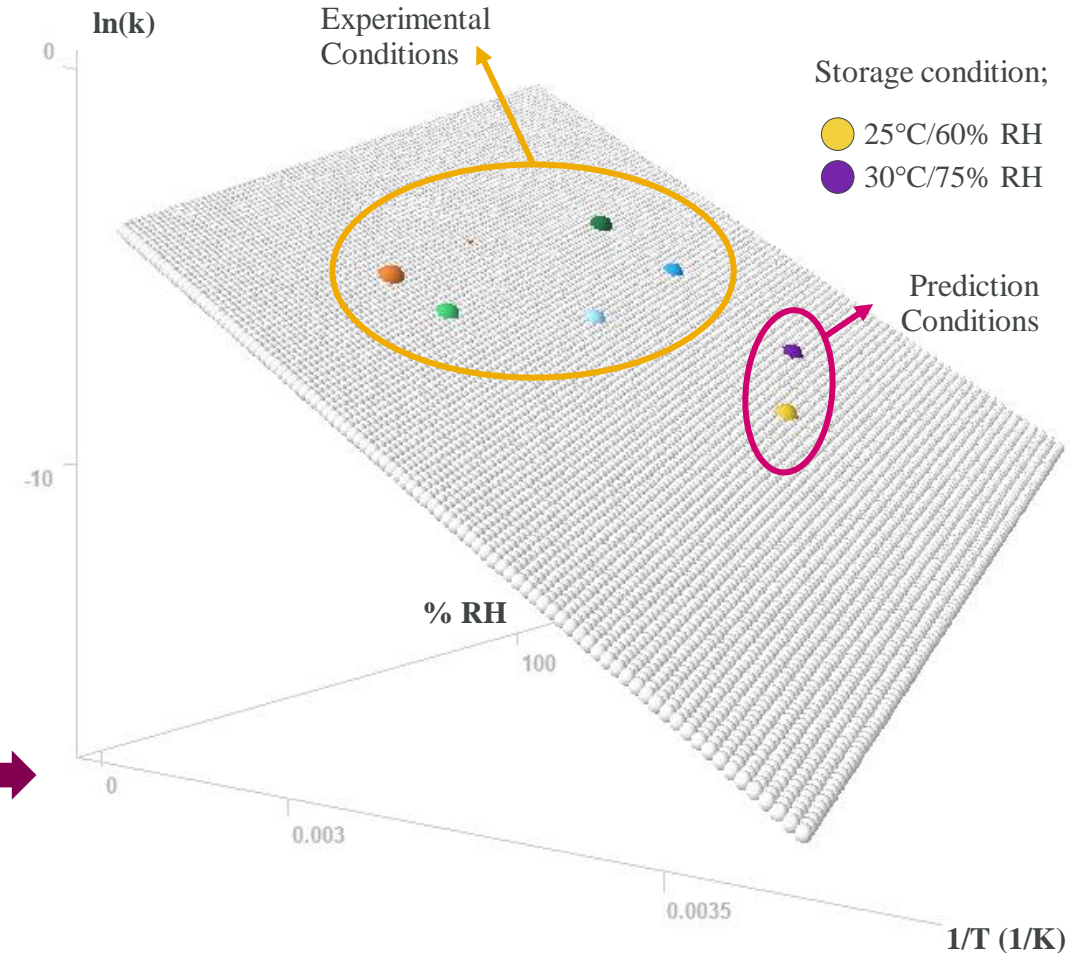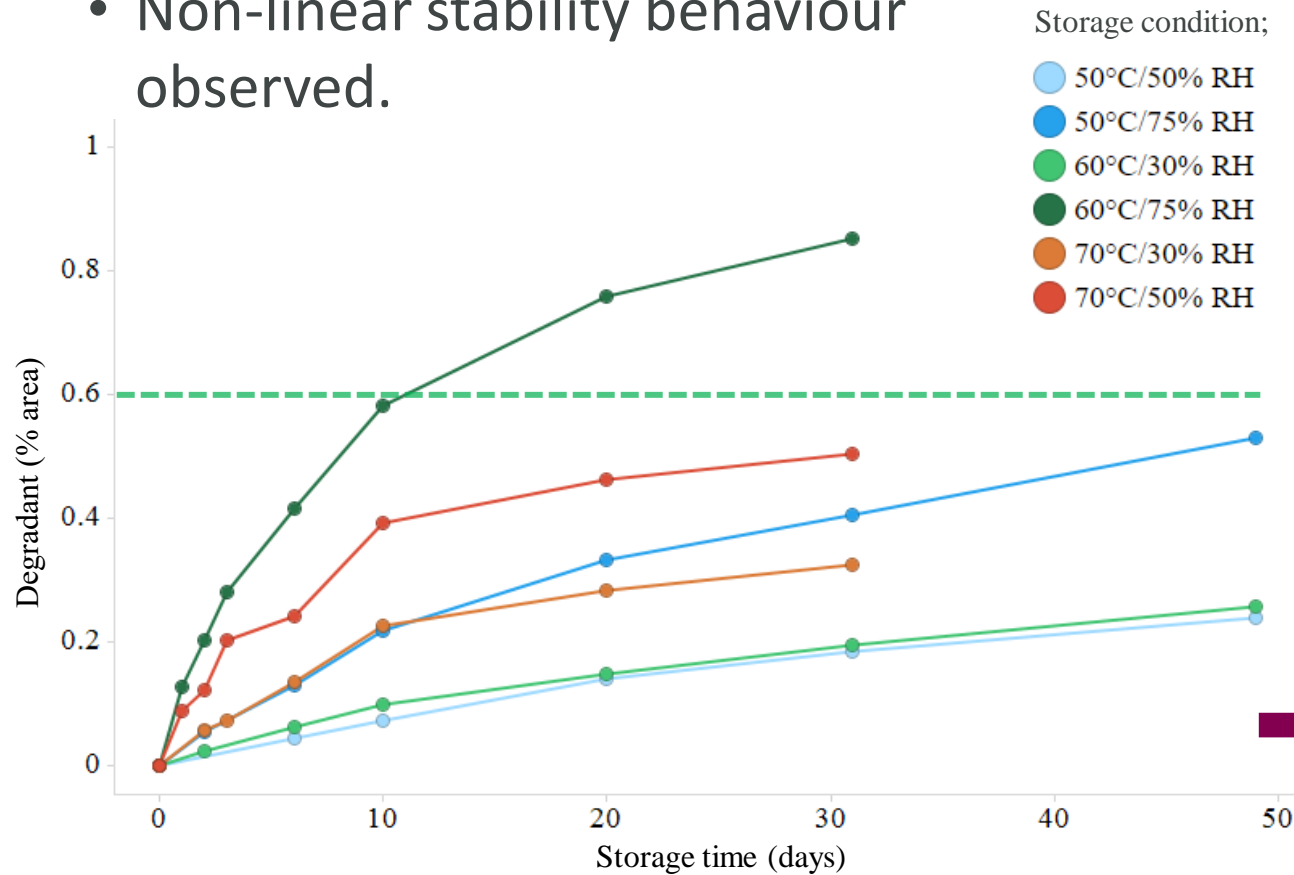- Moisture sorption understanding & *in silico* packaging predictions also carried out.

- Study duration: **49 days**.

- Study conditions: **50 – 70°C**, **30 – 75% RH**.

Case Study 3: Justification of Specifications for DP
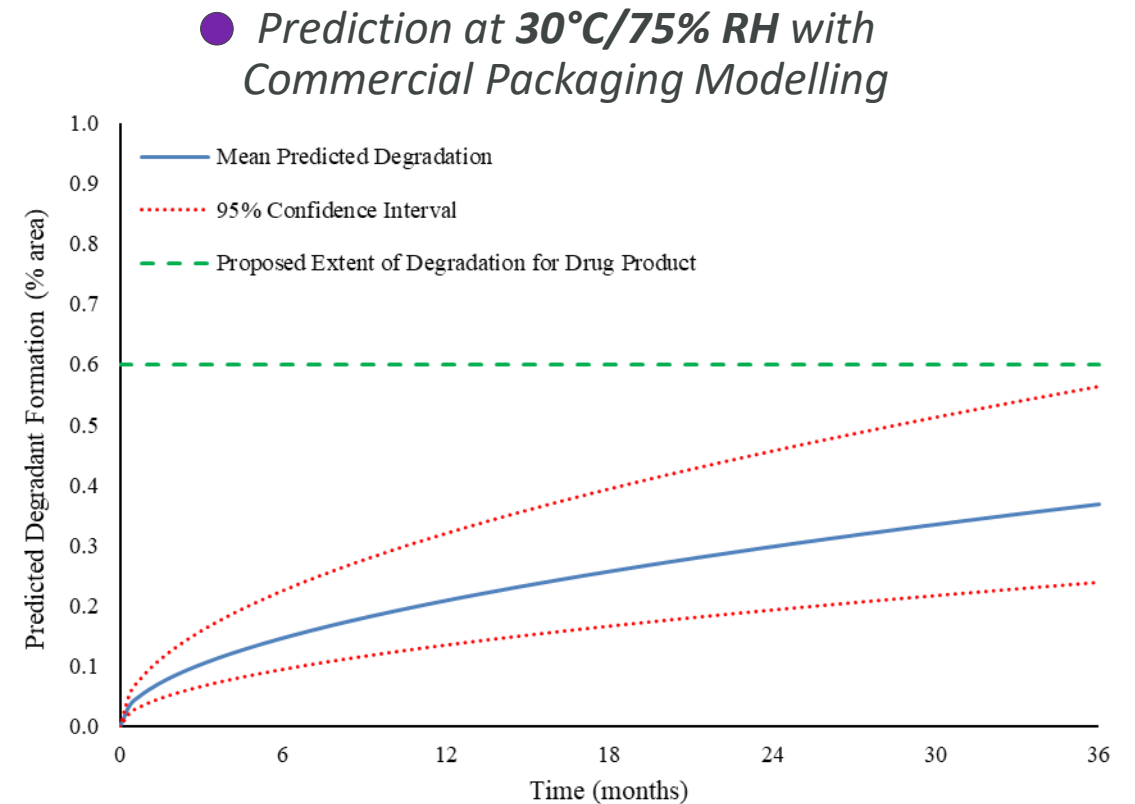## Experimental Data & Visualisation

- Non-linear stability behaviour observed.

Storage condition;
- 50°C/50% RH
- 50°C/75% RH
- 60°C/30% RH
- 60°C/75% RH
- 70°C/30% RH
- 70°C/50% RH

Storage condition;
- 25°C/60% RH
- 30°C/75% RH

ln(k)

Experimental Conditions

Prediction Conditions

% RH

1/T (1/K)

Case Study 3: Justification of Specifications for DP
Modelling & Prediction[2]

- Inclusion in *P.5.6 – Justification of Specifications for Drug Product*.

- Approach taken for 2 degradation products.

- Dedicated *P.5.5 – Characterisation of Impurities – ASAP Attachment* written.

- Wider specification limits accepted in some markets.

- Precedent for the inclusion of predictive stability in MAs.

● *Prediction at **30°C/75% RH** with Commercial Packaging Modelling*

Legend:
— Mean Predicted Degradation
⋯⋯ 95% Confidence Interval
--- Proposed Extent of Degradation for Drug Product

Y-axis: Predicted Degradant Formation (% area)
X-axis: Time (months)

Case Study 4: Feasibility Study on an Inhaled Biologic

Case Study 4: Feasibility Study on an Inhaled Biologic
## Background & Protocol

- AZ development compound – inhaled biologic formulation.

- Significant number of characterisation test methods used vs. small molecules.

- Highly hygroscopic with a low dry Tg.

- Decision to investigate feasibility of ASAP on the compound to assess applicability.

- Study duration: **8 weeks**.

- Study conditions: **40 – 70°C, 5 – 20% RH.**

- Some test methods have clear trending.

- Others were not so clear.

Test Methods	
Size exclusion Chromatography	HP-SEC
Ion Exchange Chromatography	IEC
Non-Reducing capillary electrophoresis	NR CE-SDS
Reducing capillary electrophoresis	R CE-SDS
Total Protein - UV	UV
Potency	Potency
Moisture content by Karl Fischer	KF
Modulated Differential Scanning Calorimetry	mDSC

Case Study 4: Feasibility Study on an Inhaled Biologic
Background & Protocol
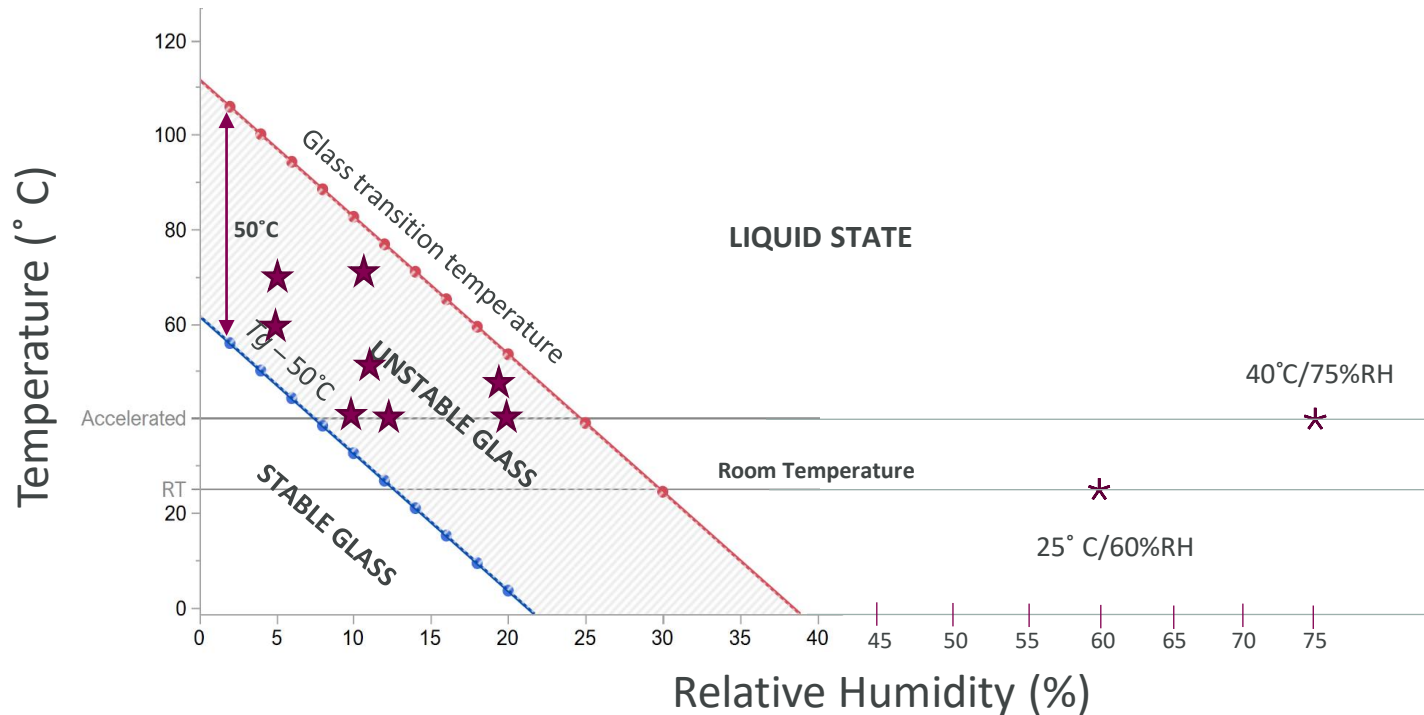
One feature of amorphous (non crystalline) solids is that their glass transition (solid to liquid phase change) is highly dependent of the water content.

Testing at standard ICH conditions is not representative of the stability of the solid phase.
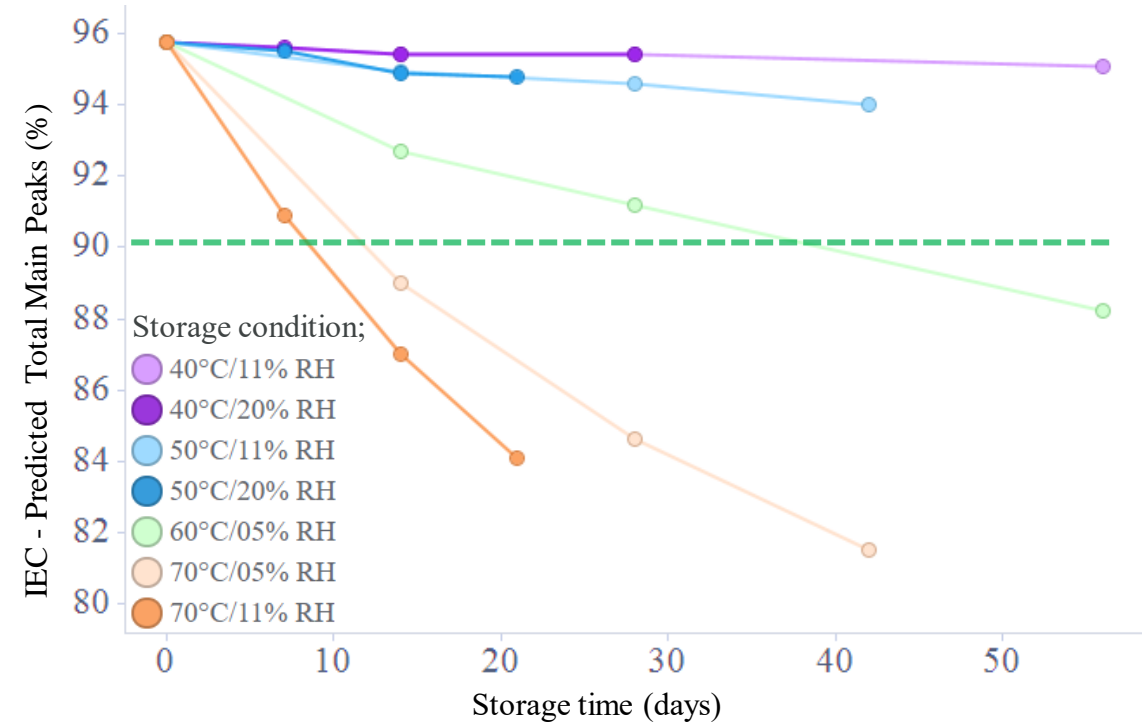
In order to test the stability of the solid phase, the testing conditions must be chosen using the glass transition as a function of storage relative humidity

29   9   David Lechuga-Ballesteros, Danforth P. Miller and Jiang Zhang. "Residual water in amorphous solids, measurement and effect on stability". In *Progress in Amorphous Food and Pharmaceutical Systems*, H. Levine, (Ed.), pp 275-316. The Royal Society of Chemistry, London, 2002.

Case Study 4: Feasibility Study on an Inhaled Biologic

Experimental Data – Ion Exchange Chromatography

- The data suggest clear trending with temperature.

- We observe that at lower temperatures, no difference due to % RH.
  - Method precision?
  - % RH range & control?

- Achieved degradation significantly less than actual spec.
  - Spec for modelling **90%**.

Storage condition;
- 40°C/11% RH
- 40°C/20% RH
- 50°C/11% RH
- 50°C/20% RH
- 60°C/05% RH
- 70°C/05% RH
- 70°C/11% RH

IEC - Predicted Total Main Peaks (%)

Storage time (days)

Case Study 4: Feasibility Study on an Inhaled Biologic

Stability Modelling[2]

1. Model quality indicators are good.

2. Model fit is reasonable for the data.

3. Some significant extrapolation required at certain conditions.
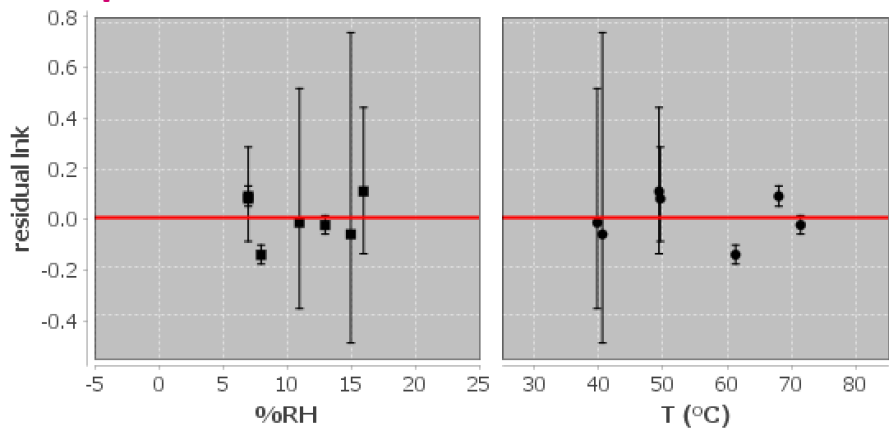
4. Some residual error in the modelling.

1

lnA	39.2
E_a	27.4 kcal/mol
B	0.0205
R^2	1.00
Q^2	0.99

2

Isoconversion Ratio: 0.10 — Extrapolation Used
Degradant vs Time; T=40, RH=11 — Time: 553.38

Isoconversion Ratio: 0.06 — Extrapolation Used
Degradant vs Time; T=41, RH=15 — Time: 478.04

Isoconversion Ratio: 0.18 — Extrapolation Used
Degradant vs Time; T=49, RH=16 — Time: 118.55

Isoconversion Ratio: 0.29 — Extrapolation Used
Degradant vs Time; T=50, RH=7 — Time: 143.12

Isoconversion Ratio: 2.22
Degradant vs Time; T=71, RH=13 — Time: 9.48

Isoconversion Ratio: 1.41
Degradant vs Time; T=61, RH=8 — Time: 39.67

Isoconversion Ratio: 2.96
Degradant vs Time; T=68, RH=7 — Time: 14.18

4

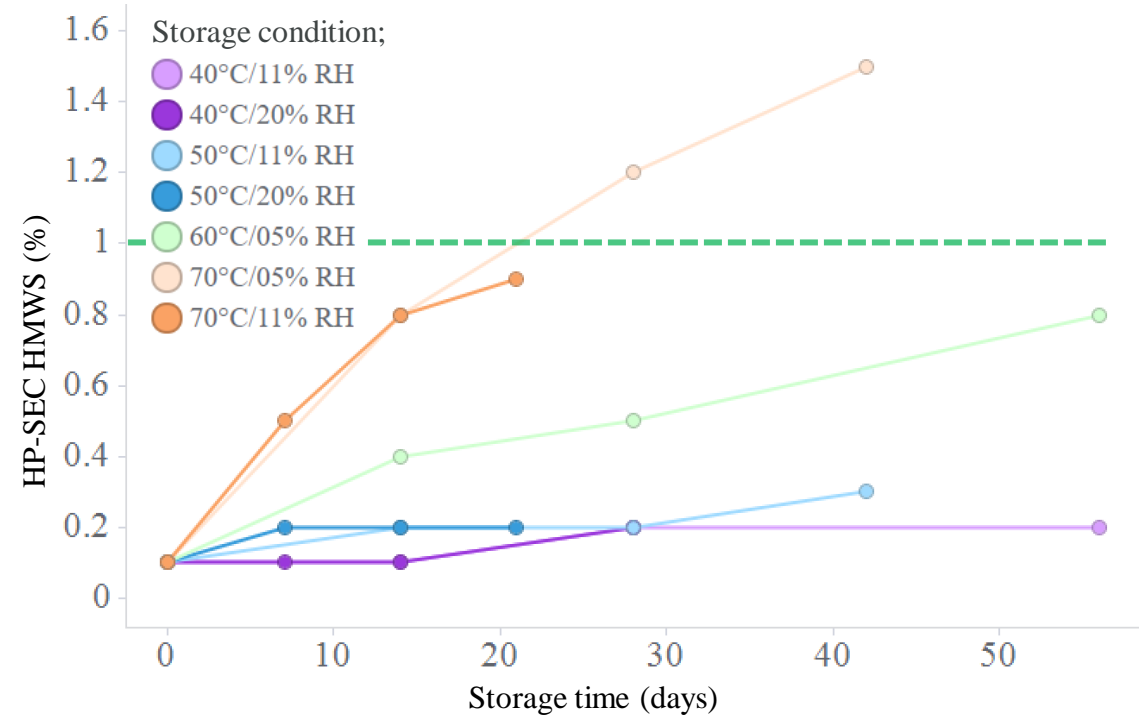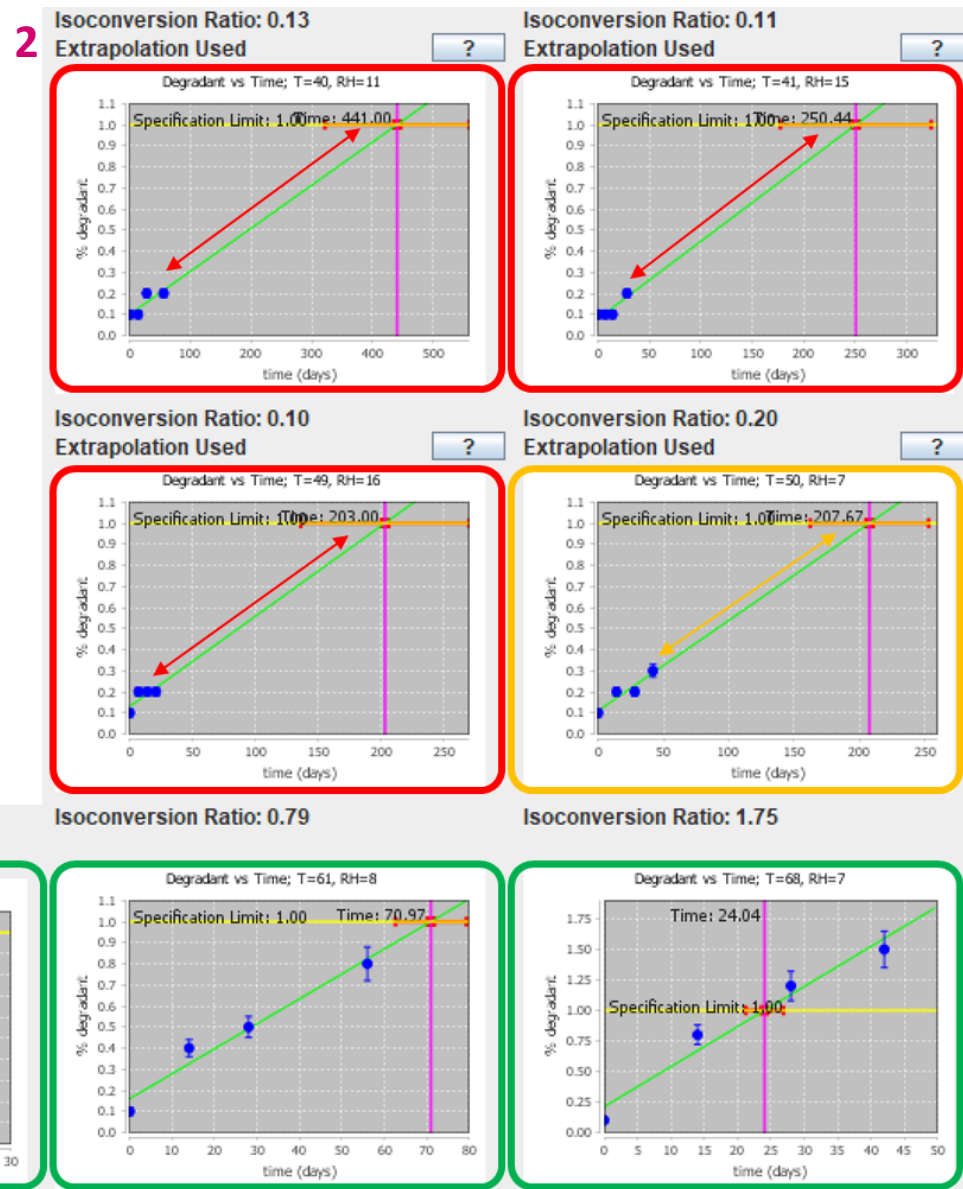# Case Study 4: Feasibility Study on an Inhaled Biologic

Results & Prediction[2]

- Prediction generated.
  - 25°C/15% RH representing an estimate of the in-pack % RH.
  - Pack configuration: Desiccated with alu-foil overwrap.
  - Further work required here.

- Overall good agreement between long term data and mean predicted rate of degradation.

Ion Exchange Chromatography - Prediction at Long Term 25°C/15% RH

Legend: Mean Predicted Degradation; 95% Confidence Interval; Specification Limit; Batch 1; Batch 2; Batch 3; Batch 4; Batch 5

X-axis: Time (months); Y-axis: IEC - Predicted Total Main Peaks (%)
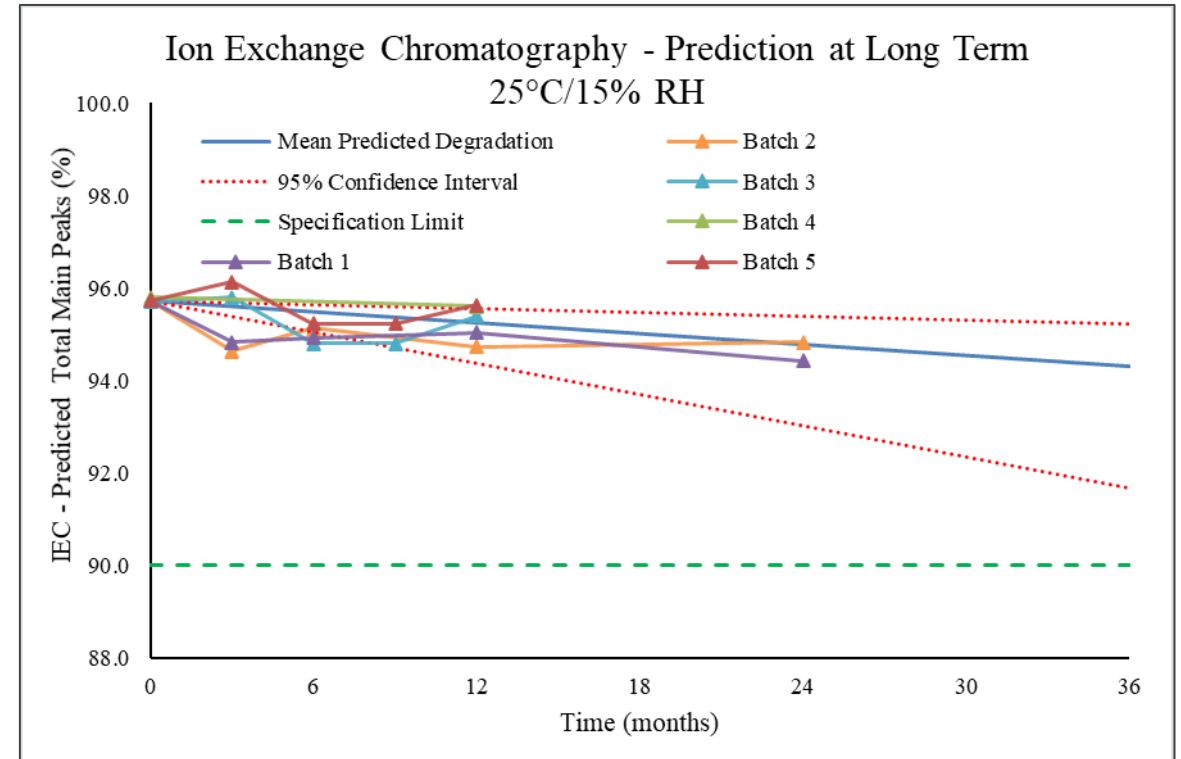
Case Study 4: Feasibility Study on an Inhaled Biologic

Experimental Data – Size Exclusion Chromatography

- Good trending of stability attribute.

- Less observed influence of % RH.
  - Again limits of the method & protocol?

- Again, achieved degradation significantly less than actual spec.
  - Spec for modelling **1%**.

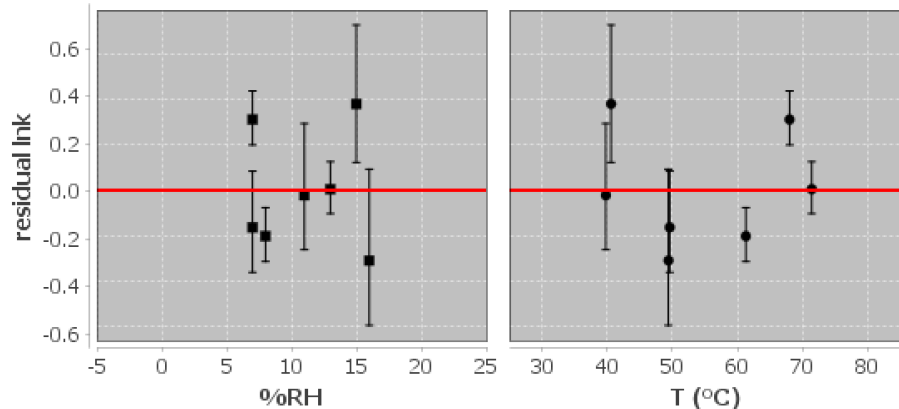# Case Study 4: Feasibility Study on an Inhaled Biologic

Stability Modelling[2]

1

lnA	25.8
E_a	20.0 kcal/mol
B	0.0208
R^2	0.95
Q^2	0.86

1. Model quality indicators are ok.

2. Model fit is reasonable for the data.

3. Some significant extrapolation required at certain conditions.

4. More residual error in the modelling.

Case Study 4: Feasibility Study on an Inhaled Biologic
Results & Prediction[2]

- Prediction generated against lower specification limit.

- Overall, good agreement with long term data.
  - Variability in longer term results noted.

Size Exclusion Chromatography - Prediction at Long Term 25°C/15% RH

Long term data points have been y-axis adjusted to align the T_0 values with the prediction (leading to one negative data point in this example).
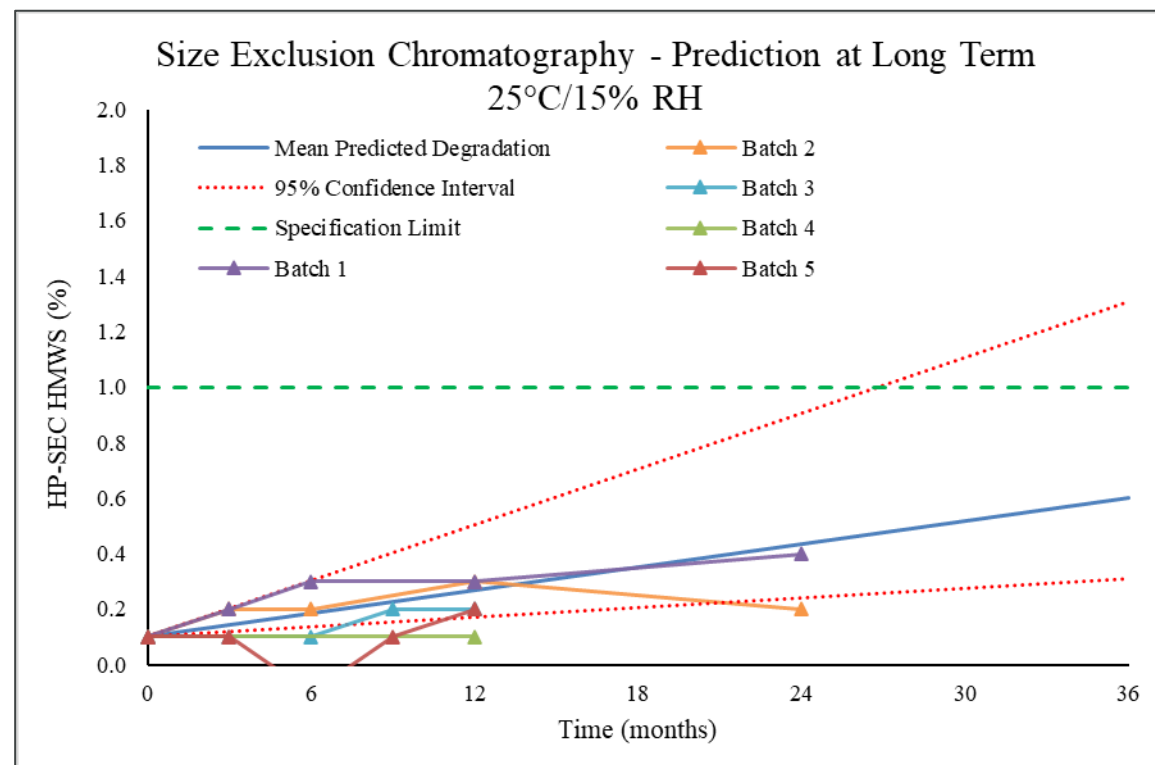
Case Study 4: Feasibility Study on an Inhaled Biologic

Conclusions, challenges & potential solutions;

- Humidity constraints and challenges with humidity accuracy.
  - Having greater control over a narrow % RH range.

- Method precision – some methods precision = 10% of the modelling spec. limit.
  - May wish to improve methods for new modalities.

- The compound is early phase, and thus specification limits are quite broad.
  - Modelling with the final specification in mind.

- Are we sure we are identifying all stability related critical quality attributes?

- **We find the Arrhenius approach to be suitable for modelling certain stability attributes of this inhaled biologic compound.**

Case Study 4: Feasibility Study on an Inhaled Biologic

Why is this important?

- Currently many of the benefits of predictive stability are not available to biologics, with maximum 2x extrapolation permitted to establish shelf-lives.

- We have started to demonstrate the potential of predictive stability in this space.

- **Impacts;**

  - Reduce the stability burden during development and keep these activities off the critical path to launch.

  - Bring life-changing medicines to the market and to <u>patients</u> more quickly.

  - Reduce the costs associated with medicines development and improve sustainability.

External Activities

External working groups

- **Innovation & Quality (IQ) Working Group** – *Science & Risk Based Stability* – Regulatory subteam.[4]

- **European Federation of Pharmaceutical Industries & Associations** (EFPIA) – *Stability Working Group.*

- **ICH Q1/Q5C Informal Working Group (IWG)** - *'Targeted Revisions of the ICH Stability Guideline Series', initiated Aug 2022*

4.   McMahon, M.E., Abbott, A., Babayan, Y. et al. Considerations for Updates to ICH Q1 and Q5C Stability Guidelines: Embracing Current Technology and Risk Assessment Strategies. AAPS J **23,** 107 (2021).
https://doi.org/10.1208/s12248-021-00641-6

External & Internal Academic

- **University of Strathclyde** – Application of Predictive Stability to model physical changes (dissolution);
  - Individual PhDs – Natalie Maclean (Completed July 2022).[5-7]
  - Community for Analytical Measurement Science – CAMS.
- **RCPE GmbH** (Graz, Austria) – Stability by Design – Chemical Degradation of Solid State Pharmaceuticals.[8] Anticipated finish Sep 2022.
- **Internal student projects** to understand other applications;
  - Chemical degradation as a function of amorphous content & pH.
  - Physical changes (dissolution).

5. Maclean, N., Khadra, I., Mann, J., Williams, H., Abbott, A., Mead, H., & Markl, D. (2021). Investigating the role of excipients on the physical stability of directly compressed tablets. *International Journal of Pharmaceutics: X*, *4*(Dec 2022), [100106]. https://doi.org/10.1016/j.ijpx.2021.100106

6. Markl, D., Maclean, N., Mann, J., Williams, H., Abbott, A., Mead, H., & Khadra, I. (2021). Tablet disintegration performance: effect of compression pressure and storage conditions on surface liquid absorption and swelling kinetics. International Journal of Pharmaceutics. https://doi.org/10.1016/j.ijpharm.2021.120382

7. Maclean, N., Walsh, E., Soundaranathan, M., Khadra, I., Mann, J., Williams, H., & Markl, D. (2021). Exploring the performance-controlling tablet disintegration mechanisms for direct compression formulations. International Journal of Pharmaceutics, 599, [120221]. https://doi.org/10.1016/j.ijpharm.2021.120221

8. Iyer, J.; Saraf, I.; Ray, A.; Brunsteiner, M.; Paudel, A. Assessment of Diverse Solid–State Accelerated Autoxidation Methods for Droperidol. Pharmaceutics 2022, 14, 1114. https://doi.org/10.3390/pharmaceutics14061114
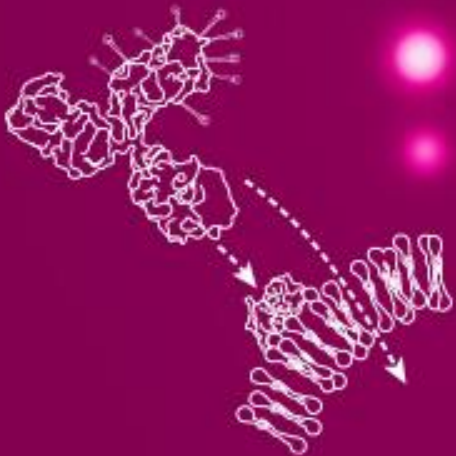
Acknowledgements

Dedication

Helen Williams

Kinder Scout, The Peak District, Derbyshire, UK – 12 August 2018

Thank you for your attention!

References.

1. Zeneth (Lhasa Ltd, Leeds, UK) – https://www.lhasalimited.org/products/zeneth.htm

2. ASAPprime v6.0.1 (FreeThink Technologies Inc., CT, USA).

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