# Practically implementing forced degradation studies

## Drug product

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**Forced degradation for pharmaceuticals**
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- **Choosing forced degradation conditions**
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- **Case study 3: excipient compatibility for a solution**

# Forced degradation of drug product
## Why?

- **Prediction of required storage conditions for long term stability**
- **Prediction of shelf life for clinical trial / commercial material**
- **Aids choice of packaging material required for ICH stability**
- **During formulation development**
  - Excipient compatability
  - Prototype formulations

# Forced degradation of drug product
## Choosing the conditions

- **Conditions chosen important**
  - Too hard hitting and start to cause secondary / tertiary degradation
  - Too soft, risk not getting any useful information from study
- **Keep in mind what the study is for**
  - If shelf life predictions required need to meet minimum requirements
  - Need conditions that discriminate between different formulations
- **Use any information about product that's already available**
  - Forced degradation on drug substance
  - Long term stability studies on product
  - Stability information on previous formulation type's
- **Remember – excipients may degrade at lower temperatures than the API**
  - If possible also set down individual excipient of concern to make sure doesn't interfere with API (e.g. in chromatography)
- **What analysis is required?**
  - Chromatography for chemical degradation
  - Spectroscopic techniques to assess physical changes
  - Photographs, measurement of oxygen in the headspace...

# Forced degradation of drug product

## Example protocols

- **Example protocol for prototype tablets where API and capsule formulation are known to be chemically stable (no degradation at 40ºC/ 75% RH for 6 months). Analysis by UHPLC only.**

| | 50ºC/75% RH | 70ºC/30% RH | 70ºC/75% RH | 80ºC/80% RH | 90ºC/25% RH |
|---|---|---|---|---|---|
| initial | x | | | | |
| Day 7 | x | x | x | x | x |
| Day 14 | x | x | x | x | x |
| Day 21 | x | x | x | o | o |
| Day 28 | x | x | x | | |

| | 25°C/60%RH | 40°C/10%RH | 40°C/75%RH | 50°C/30%RH |
|---|---|---|---|---|
| Initial | x | | | |
| 7 days | x | x | x | x |
| 14 days | x | x | x | x |
| 1 month | x | x | x | x |
| 2 months | o | o | o | o |

- **Example protocol for excipient compatibility of respiratory formulation known to be unstable. Analysis by UHPLC, Raman, NIR and images.**

X = pull sample, O = optional pull

# Practical implementation of studies

## Automated stability system

- **Some drug product studies, especially during formulation development, can be VERY large**
  - 10-15 variants, 5 stability conditions x 5 time points = hundreds of samples!
- **Within different project teams can have little previous knowledge of running forced degradation studies**
- **Answer = Central automated system with 1 or 2 operators for all forced degradation studies**
- **At AZ Macclesfield have such a tool. Bespoke automated system made by RPD tool (Switzerland).**

# Practical implementation of studies

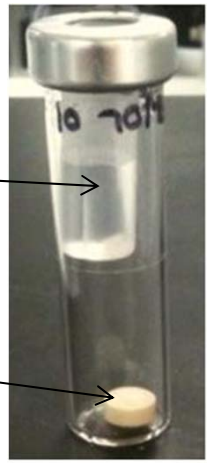
## Automated stability system

- **Individually controlled racks with possible temperature range from approx. 10-100ºC**

- **Humidity controlled separately for each sample with saturated salt solutions**

- **Online UHPLC analysis with sample preparation and UV, MS and ELSD Detection for chemical degradation**

- **Online NIR and Raman analysis for physical changes on stability**

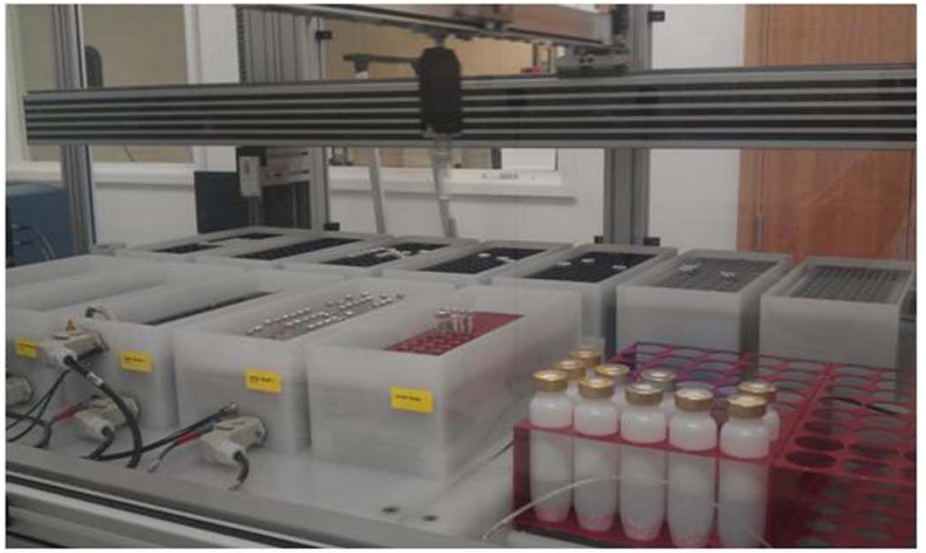



- **Online camera for visible changes in sample**

- **Oxygen sensor to monitor uptake of oxygen in the vial headspace**

# Practical implementation of studies

## Automated stability system



# Case study 1: Tablet excipient compatibility

## Background

- **Oncology project in phase I that required an immediate release tablet formulation for future clinical studies**

- **Design of Experiment technique used to make 16 prototype formulations containing different excipients for fillers, disintegrent, binder, glidant and lubricant**

- **Levels of each of the excipients and the API were kept constant**

- **Forced degradation required to rank the prototype formulations and assess which excipients may cause degradation of the API**

- **Need to provide recommendation of which excipients to take forward to stage 2 – quantitative formulation development**

# Case study 1: Tablet excipient compatibility

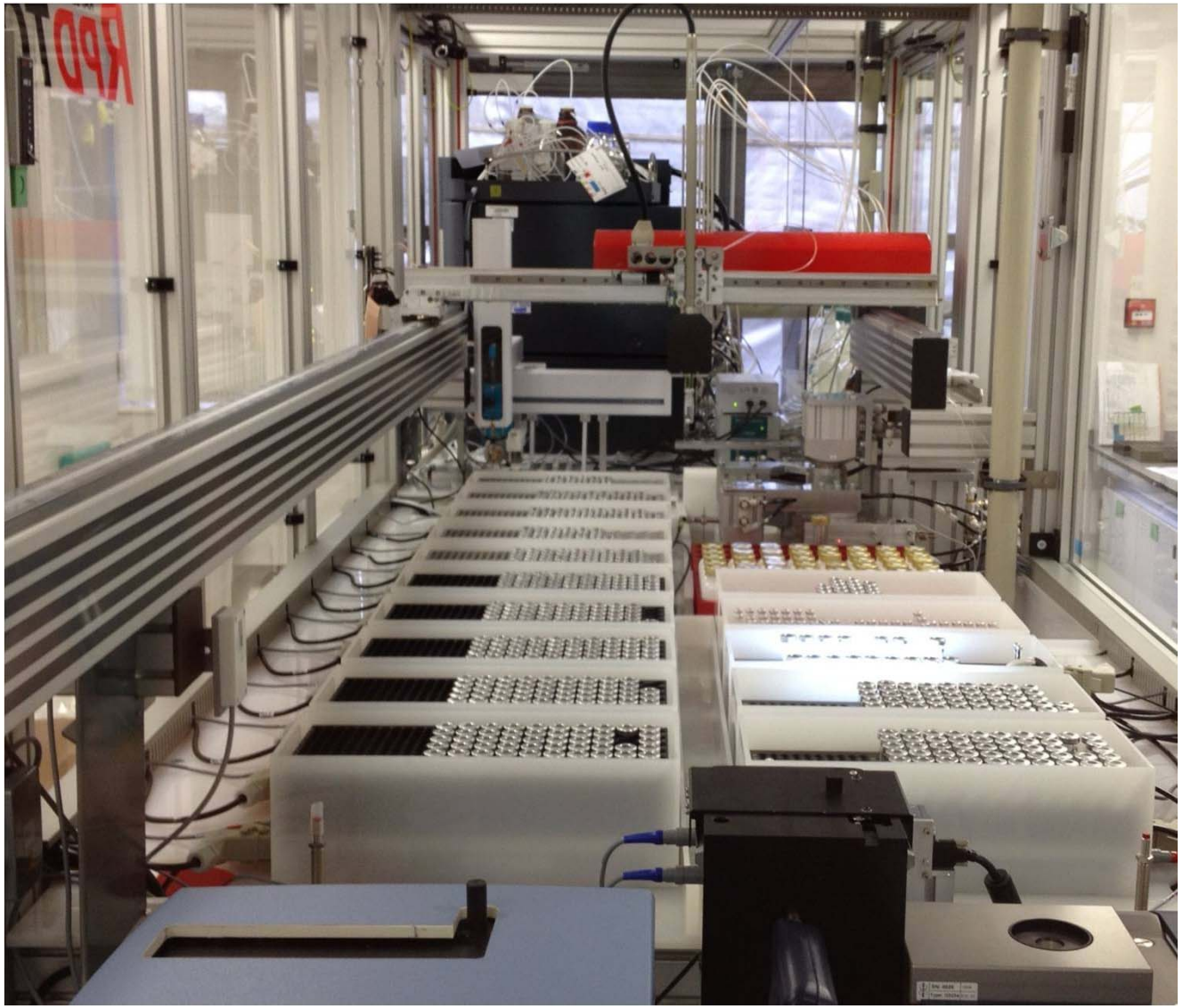
## Experimental

- **Previous knowledge on project shows that API is extremely stable**
  - Very little degradation seen even under forcing conditions
  - In order to rank formulations – need to observe some degradation
  - Shelf life predictions not required as prototypes won't be the same as final formulation

| | 40°C /75% RH | 70°C/11% RH | 70°C/75% RH | 90°C/11% RH |
|---|---|---|---|---|
| initial | x | | | |
| Day 3 | | x | x | x |
| Day 7 | o | x | x | x |
| Day 14 | o | x | x | x |
| Day 21 | o | x | x | x |
| Day 28 | o | x | x | x |

- **Analysis by UHPLC at each time point using UV detection. A small number of formulations were also analysed by Raman and NIR to monitor any physical changes**

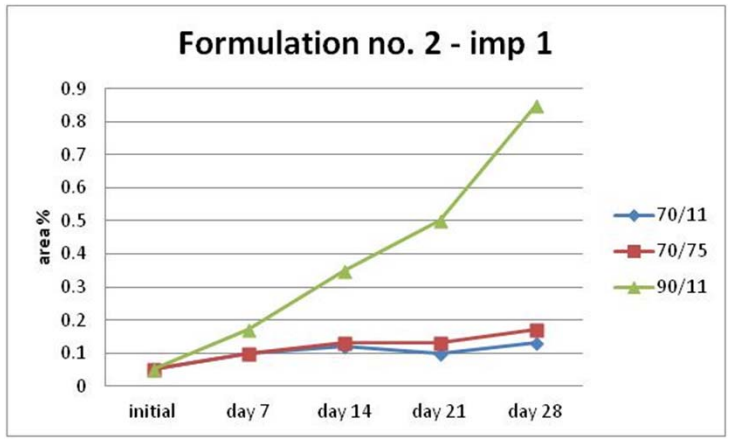
- **Samples stored at 40 °C/75% RH will only be analysed if large amounts of degradation seen at other conditions**

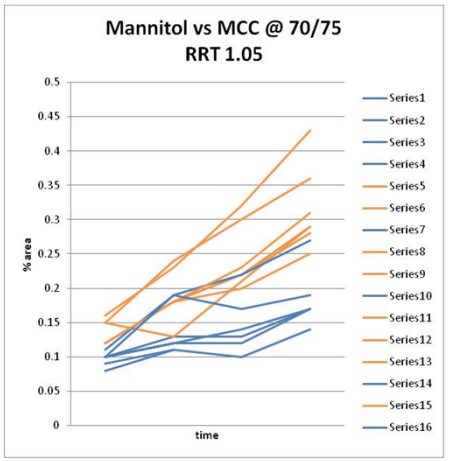


# Case study 1: Tablet excipient compatibility

## Results

- **Four main degradation products found in all batches**
- **Some ranking of formulations possible**
- **Differences between excipients observed e.g. For primary fillers, MCC found to cause greater degradation than Mannitol**




MCC

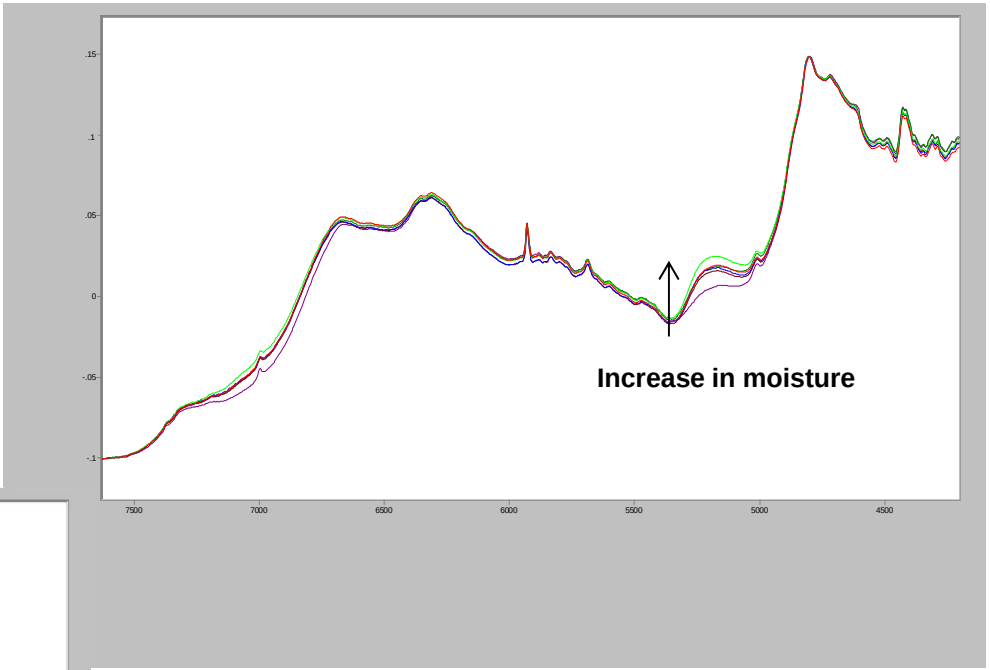
Mannitol

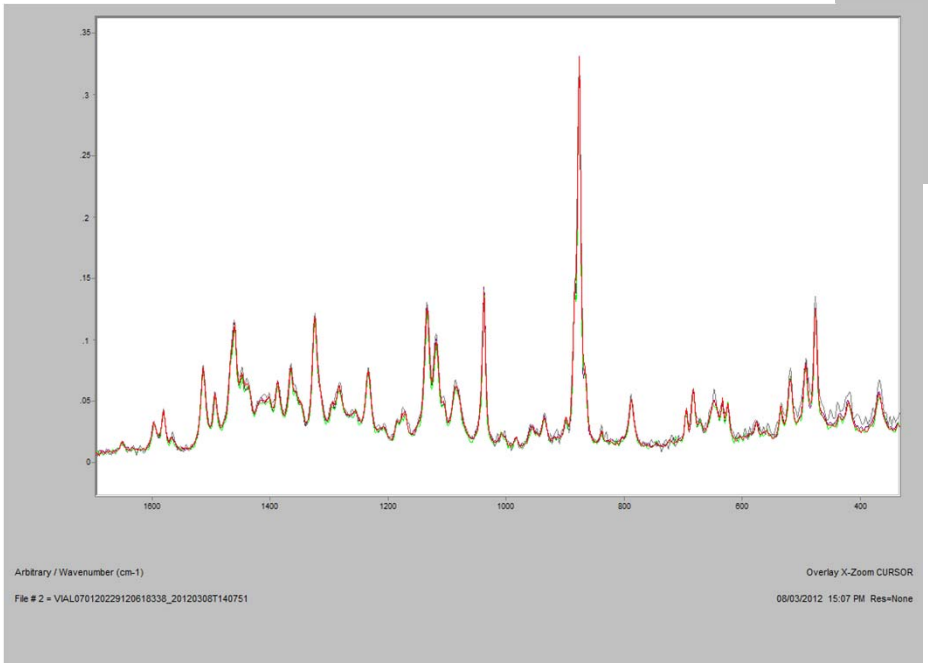
- **<u>However large amount of degradation seen for all formulations</u>**
  - Problem with all formulations that must be due to process, API used or drug loading of tablets and not the individual excipients

# Case study 1: Tablet excipient compatibility

## Results

**Assessment of NIR and Raman shows no change in physical form over the study for the tablets analysed at 70°C / 75% RH**



# Case study 1: Tablet excipient compatibility

## Conclusion

- **Unexpected chemical degradation results**
- **Not possible to recommend any excipients to take forward to stage 2**
- **Conditions chosen in protocol too harsh for prototype formulations**

- **<u>BUT...</u>**

- **Study shown that fundamental issue with current formulation within a short 4 week study**

- **Better to find out now rather than later down the line**
  - might not have seen as much of a problem if 'softer' conditions were chosen

- **Outcome: further work done on formulation development and now have much more stable formulation with at least 2-3 years room temperature shelf life**

- **Without the automated system much less data would be available for these formulations – may of missed the inherent instability!**

# Case study 2: predicting shelf life

## Background and protocol

- **Oncology project moving to phase IIb**

- **Tablet known to be unstable – but shelf life and required storage condition unknown**

- **Room temperature storage required for patient packs in clinic – at least 6 weeks**

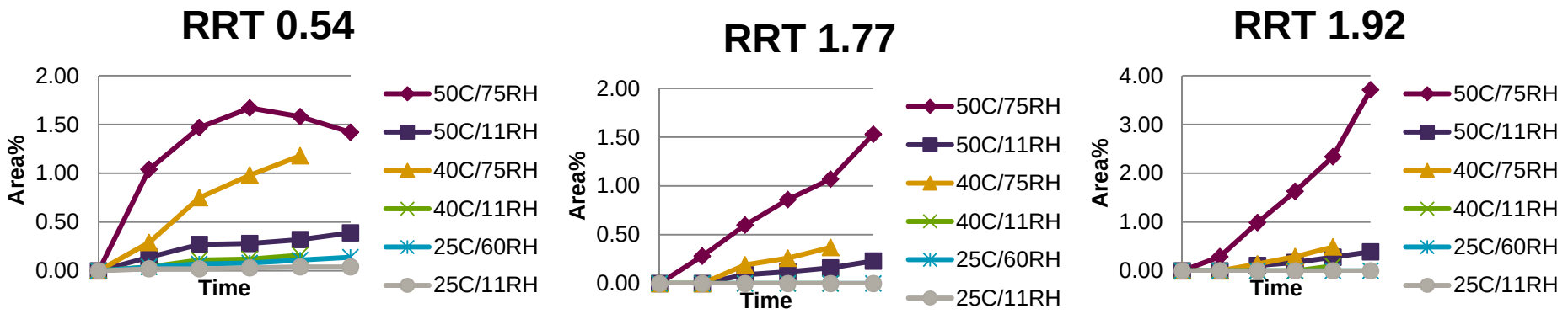
- **Forced degradation study required to predict shelf life of tablet and recommend a long term storage condition**

| | *25* /11 | *25/60* | *40* /11 | *40/75* | *50* /11 | *50/75* |
|---|---|---|---|---|---|---|
| *Initial* | *x* | | | | | |
| *Day 3* | *x* | *x* | *x* | *x* | *x* | *x* |
| *Day 7* | *x* | *x* | *x* | *x* | *x* | *x* |
| *Day 10* | *x* | *x* | *x* | *x* | *x* | *x* |
| *Day 14* | *x* | *x* | *x* | *x* | *x* | *x* |
| *Day 21* | *o* | *o* | *o* | *o* | *o* | *o* |

# Case study 2: predicting shelf life

## Results

- **Three degradation products observed**




- **Mostly linear degradation except for RRT 0.54 at the harshest condition that plateau's off**
  - Slow in rate or secondary degradation occurring, this data will be used with caution for the predictions

# Case study 2: predicting shelf life

## OSP tool

- **OSP tool (Open Stability Predictor) is internal software that uses the modified Arrhenious equation to predict the degradation at a pre-defined temperature and humidity**

$$\ln k = \ln A + Ea/R*[1/T] + B*[\%RH]$$

- T = temperature (K)
- RH = relative humidity (%)
- k = rate constant

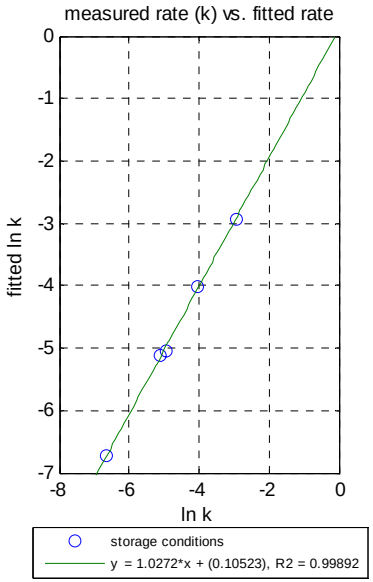
- A = pre-activation constant
- Ea = activation energy
- R = molar gas constant
- B = moisture coefficient

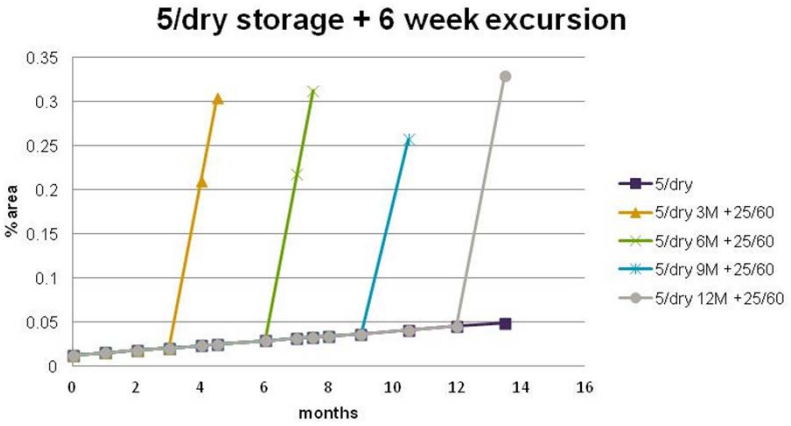
- **The tool uses a number of outputs to show the user how good a model the OSP has been for the data used and therefore how trustworthy the prediction is**

# Case study 2: predicting shelf life

## Predictions – RRT 0.54

- **Shown to be the shelf life limiting impurity**
- **The measured vs fitted rate plot is used to show how good the model is**
  - Just one point not evenly spaced along the line compared to others
  - Prediction mostly trustworthy
- **Predictions show that long term storage at room temperature is not possible**
  - Refrigerated storage with dessicant should give at least a 2-3 year shelf life
- **Can be predicted that required 6 weeks at room temperature after refrigerated storage should not result in the degradation product reaching the specification level of 0.5%**



# Case study 2: predicting shelf life

## Conclusion

- 3 week accelerated stability study has shown that long term room temperature storage not possible for this product

- Recommended packaging for this formulation includes desiccant as degradation greatly increases in the presence of moisture

- Gives confidence that 6 week excursion at room temperature in the clinic will not result in the impurities going above specification level – no safety concerns

- Use of the automated system saved resource compared to doing the study manually

# Case study 3: Solution excipient compatibility

## Background

- **Anti-obesity product in phase I**
  - Formulation for multi-dose injection required for later clinical trials and commercial
- **Liquid formulation containing preservative and other excipients to control the pH etc**
  - 18 prototype formulations made in total
- **Which excipients / preservatives to take forward for further development work based on chemical stability?**
- **Ideally have 2-3 year room temperature storage for final formulation**

# Case study 3: Solution excipient compatibility

## Experimental

- **The formulations contained various acids and preservatives at different concentrations. All other variables were kept constant**

| Acid | Preservative |
|---|---|
| Acetic acid | Benzyl alcohol |
| Citric acid | Phenol |
| Tartaric acid | m-cresol |
| | EDTA |

- **No humidity control required for these aqueous solution formulations**

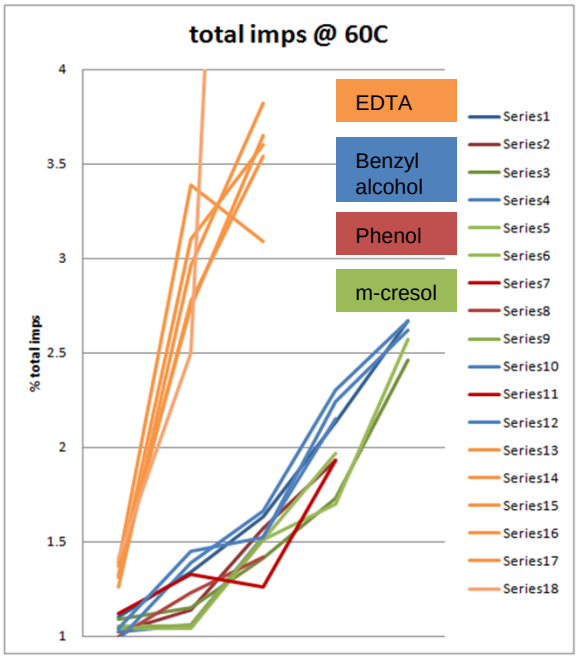
| | 40°C | 50°C | 60°C | 70°C |
|---|---|---|---|---|
| Initial | x | | | |
| Day 4 | x | x | x | x |
| Day 7/11 | x | x | x | x |
| Day 14 | x | x | x | x |
| Day 21 | x | x | x | x |
| Day 28 | x | x | x | |

- **Samples tested by UHPLC only at each time point**

# Case study 3: Solution excipient compatibility

## Results

- **Three main degradation products observed**
- **Major observation during study was that presence of EDTA resulted in a large amount of degradation**
  - No significant difference between the different acids used
- **OSP tool used to give guidance on likely storage conditions for final formulation**
  - Room temperature storage predicted to be ok for the majority of the formulations not containing EDTA



# Case study 3: Solution excipient compatibility

## Conclusion

- **Clear guidance to project to not continue with development of a formulation containing EDTA**

- **Use of automated system saved at least the resource of 1 person for a whole month if not longer**

- **Confidence gained from predictions that formulation can be made that satisfies shelf life requirements at this early stage**

# Summary

- **Number of reasons for doing forced / accelerated stability studies on drug product**
  - Gives early indication of shelf life and storage conditions
  - Use to rank prototype formulations
  - Used for chemical excipient compatability

- **Use of an automated system**
  - Allows more studies with less resource
  - More information from each study as more time points/ conditions are possible
  - Specialist team for accelerated stability – better study design etc