

ASAP Regulatory Strategy, Acceptance and Feedback

AstraZeneca perspective

Helen Williams

SOS 2016, New Jersey, 26th September



ASAP Regulatory Strategy, Acceptance and Feedback – An AstraZeneca Perspective

Overview

- RPD Tool
- MHRA Technical Presentation
- ASAP Regulatory Case Studies
 - 1 – Capsule to tablet change
 - 2 – New formulation, common granule
 - 3 – New formulation, not common granule
- Packaging examples
- Ongoing strategy



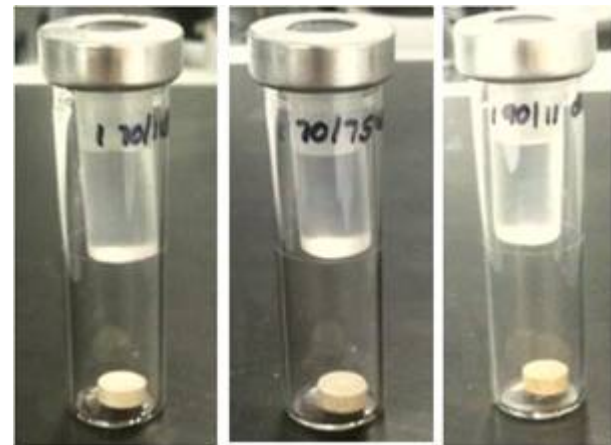
Rapid Product Development Tool

Performing ASAP Studies



- Heated racks
- Saturated salt solutions for RH
- 1000 vial capacity
- LC-UV, LC/MS, NIR, Raman
- Automated sample prep and analysis
- Formulation screening
- Purchased in 2011

On-site ASAP training from Ken Waterman in March 2014.



MHRA Technical Presentation

We were invited to give a technical presentation to the MHRA in July 2014 on ASAP and Packaging Predictions.

Feedback ASAP Stability Testing

- Receptive to the idea
- Want to get used to reviewing it in submissions alongside standard stability data
- Legitimate concerns, want more information/evidence and experience of this type of data before they will be completely comfortable
- Keen for mass balance to be demonstrated
- Some acceptance that this could help reduce stability burden for minor changes eg. tablet coat.
- Clear concern about continuing to monitor product performance eg. dissolution and physical integrity

Feedback Packaging Predictions

- Packaging side well received, no concerns voiced



ASAP Case study 1 – Change from capsule to tablet formulation, 2013

Background

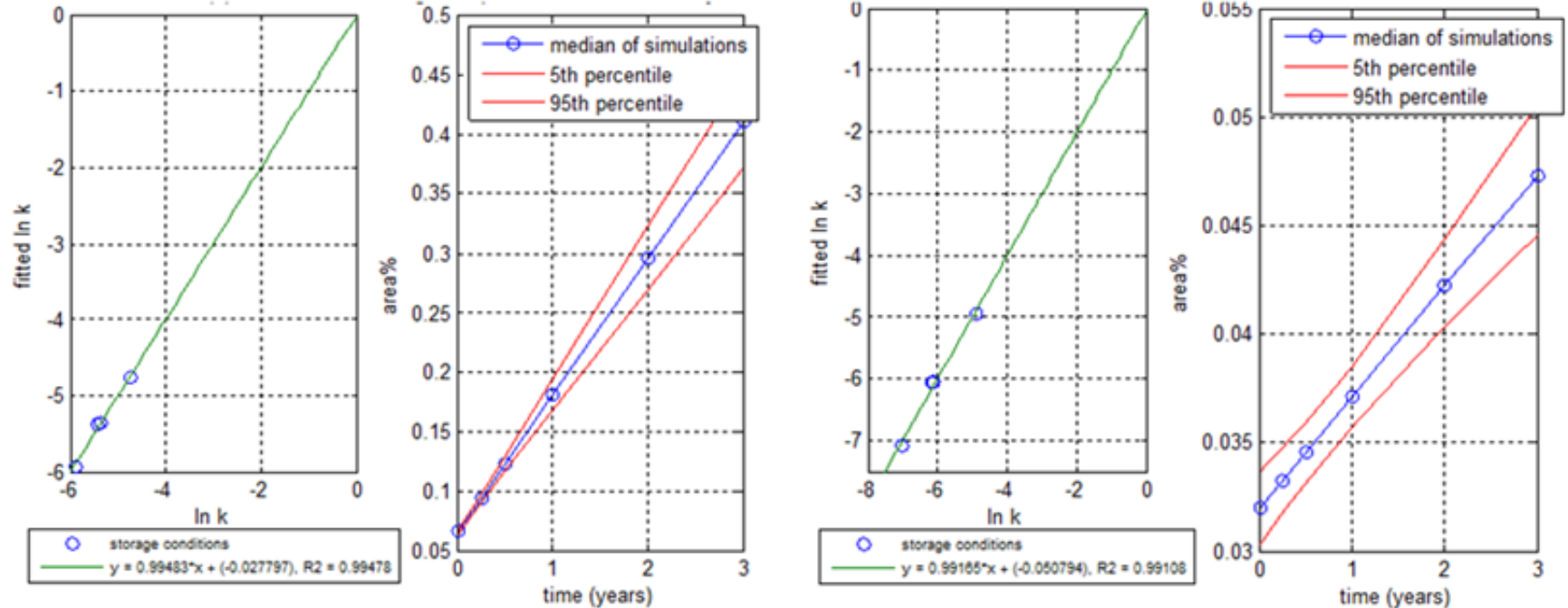
- Existing stable capsule formulation, tablet formulation required
- Formulation screen ASAP study was performed on RPD tool
- One main degradant

- Only 2 week real time tablet stability data was going to be available for the Phase 1 bridging IVIVR submission
- Predicted stability data from the ASAP study was therefore included in the submission
- Dissolution studies were also performed to support the shelf life claim (40°C/75% RH open for up to 12 weeks)



ASAP Case study 1 – Change from capsule to tablet formulation

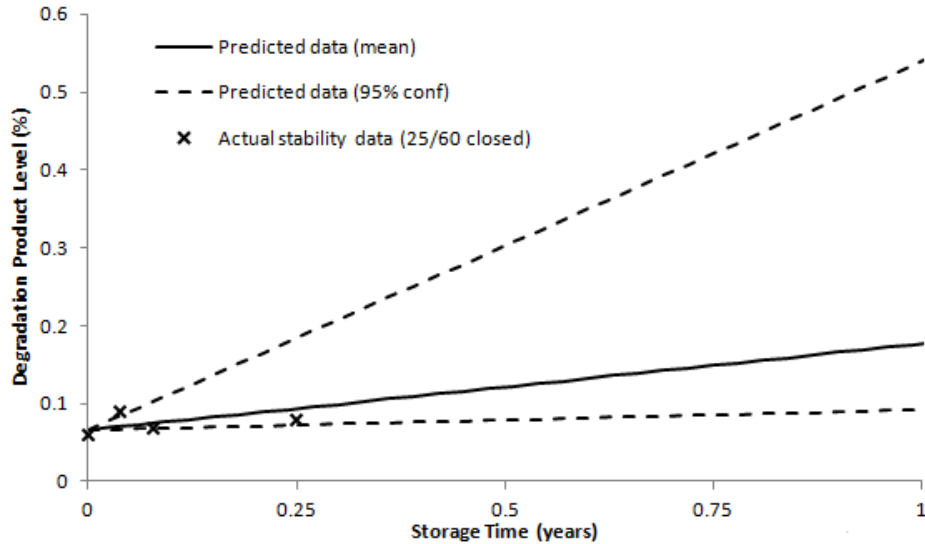
Figure 1 Measured rate versus fitted rate plot and Predicted degradation plots for (i) Smiles 1 and (ii) Smiles 2



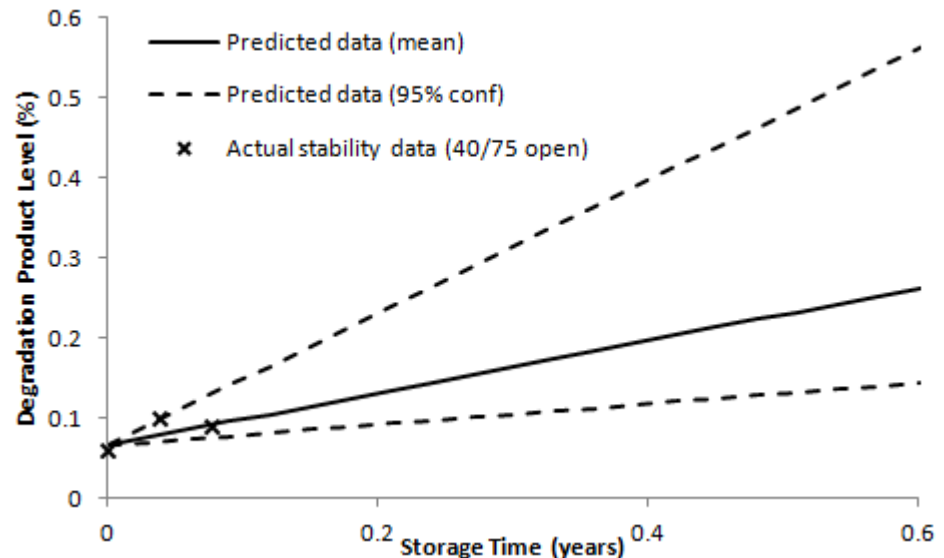
The models predicted an overall increase of 0.05% Area for the main degradant after 6 months stored open at 25°C/60% RH. Therefore an initial shelf life of 6 months was proposed. The submission was accepted by the MHRA with no questions.



ASAP Case study 1 – Change from capsule to tablet formulation



Comparison of predicted data (open) with subsequent real time stability data at 25°C/60% RH (packed) and 40°C/75% RH (open).



ASAP Case study 2 – New formulation from common granule, 2015

Background

- three different tablet strengths (common granule)
- stable product
- 5 year shelf life at 25°C/60% RH
- developing a new low strength tablet (common granule) with only 3 months real time stability data available at time of submission
- performed ASAP study using crushed tablet – worst case, increased surface area

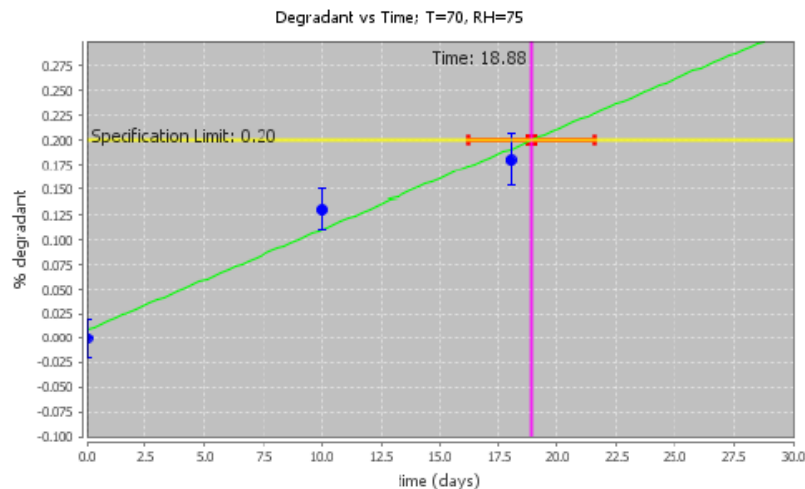
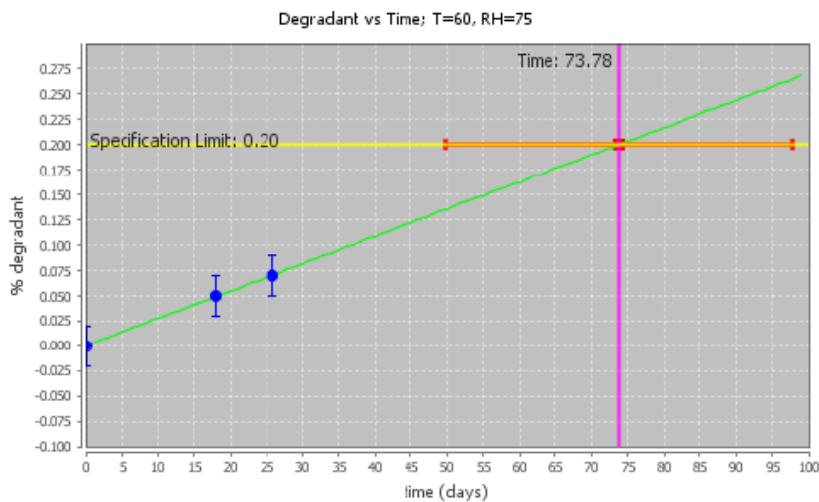
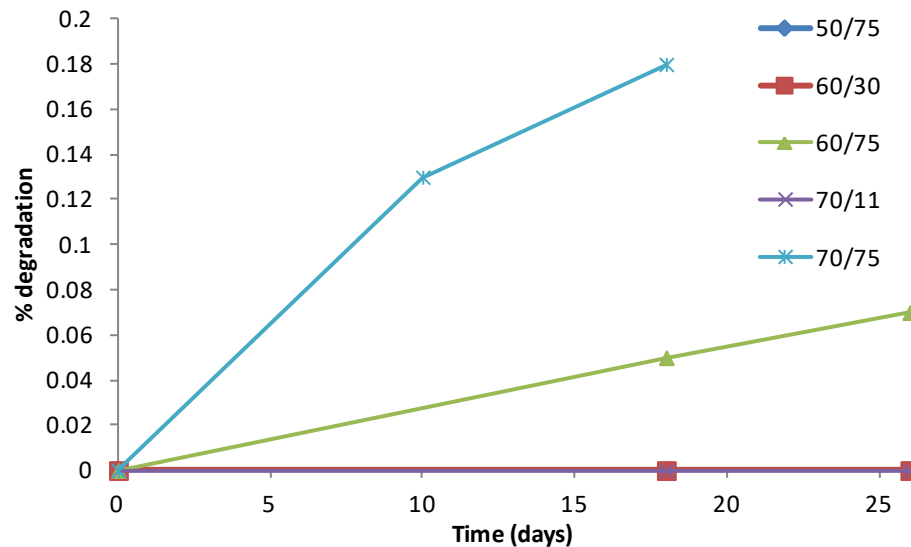
NB the aim to take a sample to specification limit may not always be possible for a stable product



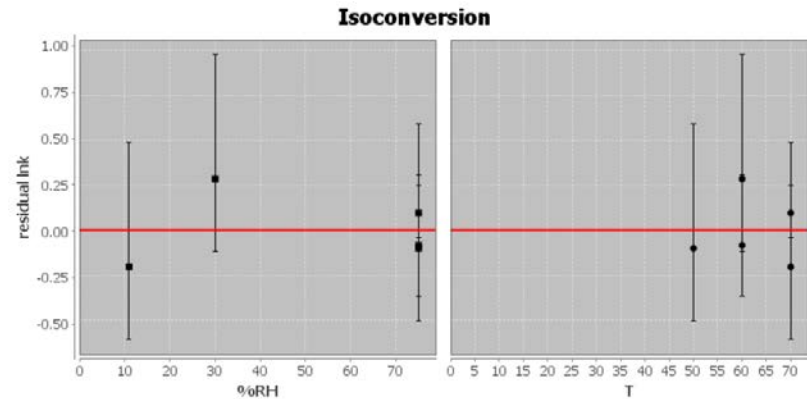
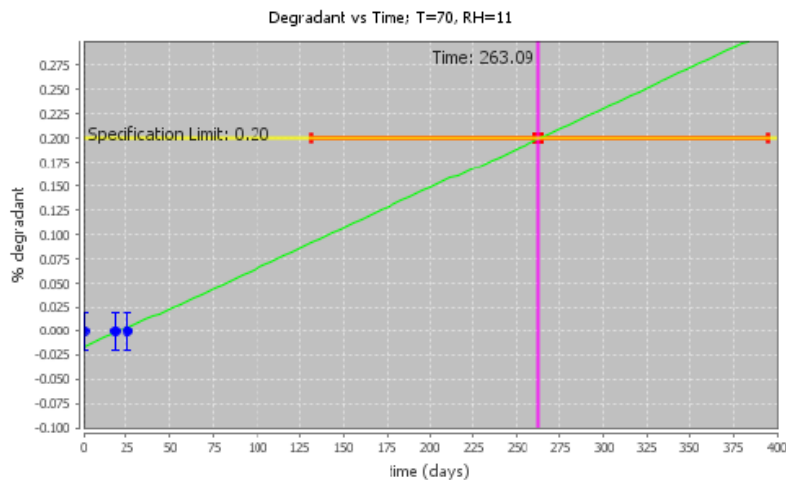
ASAP Case study 2 – Common Granule

Storage Condition (°C/% RH)	Storage time (days)			
	0	10	18	26
Initial	X - triplicate			
50/75			X	X
60/30			X	X
60/75			X – 5 fold repeat	X
70/11			X	X
70/75		X	X	

X = analysis time point



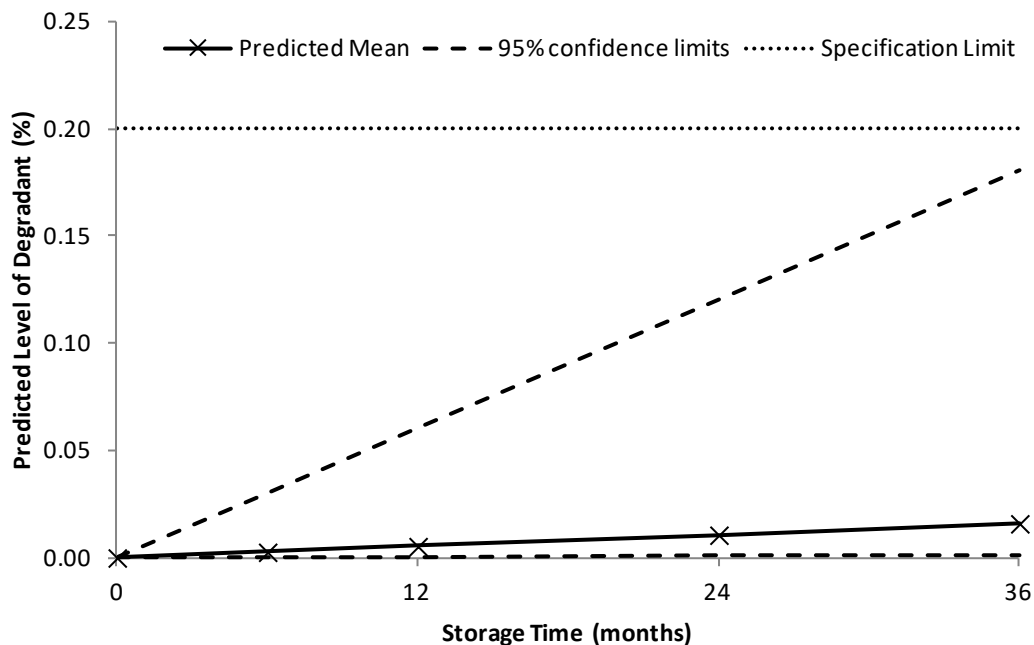
ASAP Case study 2 – Common Granule



InA	32.0	±	9.0	
E _a	26.8	±	6.0	kcal/mol
B	0.0365	±	0.0088	
R ²	0.97			



ASAP Case study 2 – Common Granule

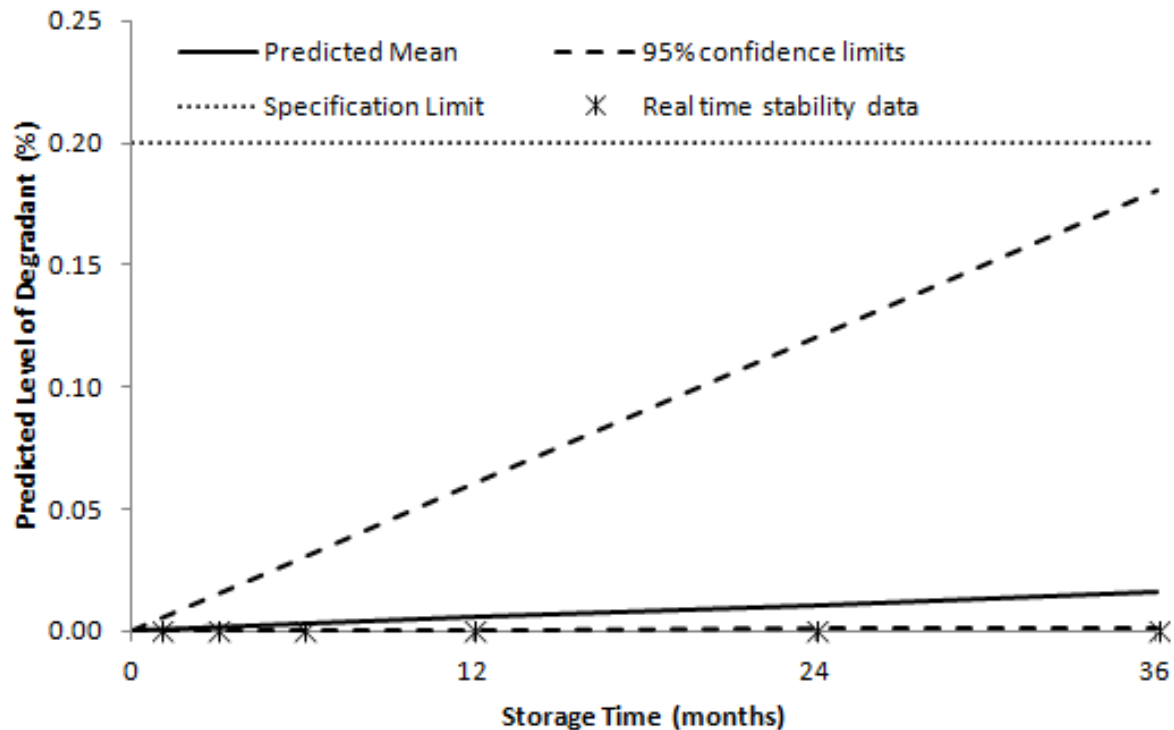


- This ASAP study data was used to support a 3 year shelf life claim based on just 3 months real time stability data for this low strength formulation.
- The ASAP data was submitted to the USA, UK, France, Italy, Turkey, Egypt, Lebanon and Kenya
- Accepted with no questions.



ASAP Case study 2 – Common Granule

Comparison with long term stability data for higher strength formulation



ASAP Case study 3 – Low strength formulation, not common granule, 2015

Background

- New low strength tablet formulation
- Two existing higher strength stable tablet formulations with 24 month stability data, 36 month shelf life
- New formulation had different drug load, different excipient ratios, different colour coating

Time point	60°C/30% RH	60°C/75% RH	70°C/11% RH	70°C/75% RH	80°C/30% RH
Day 14			X	X	X
Day 28	X	X	X	X	X

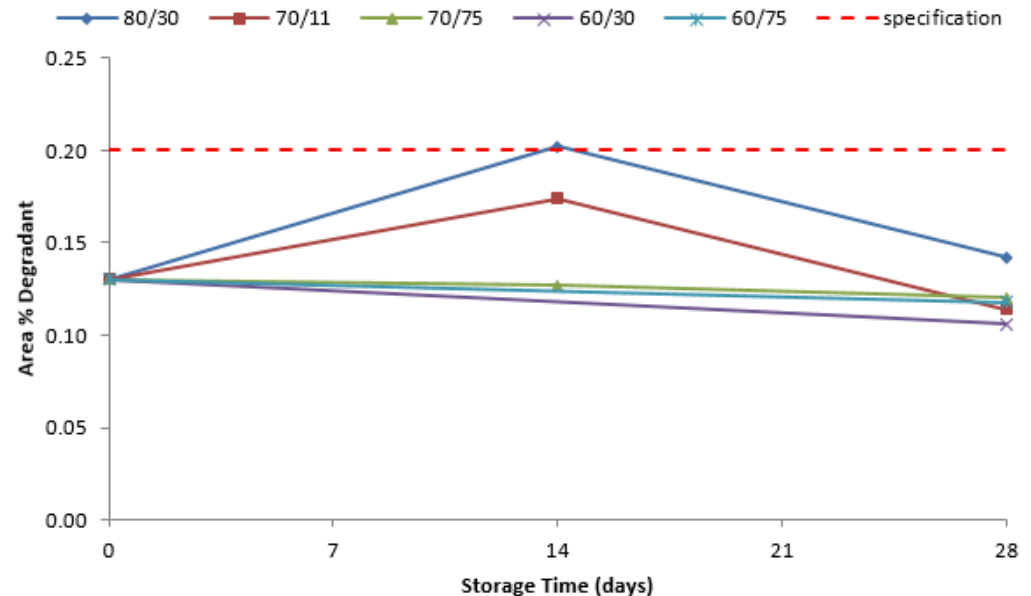
X Analysis time point.

- Also included enantiomeric purity stressed study, confirmed no risk of chiral conversion
- Relied upon dissolution data for existing higher strength formulations



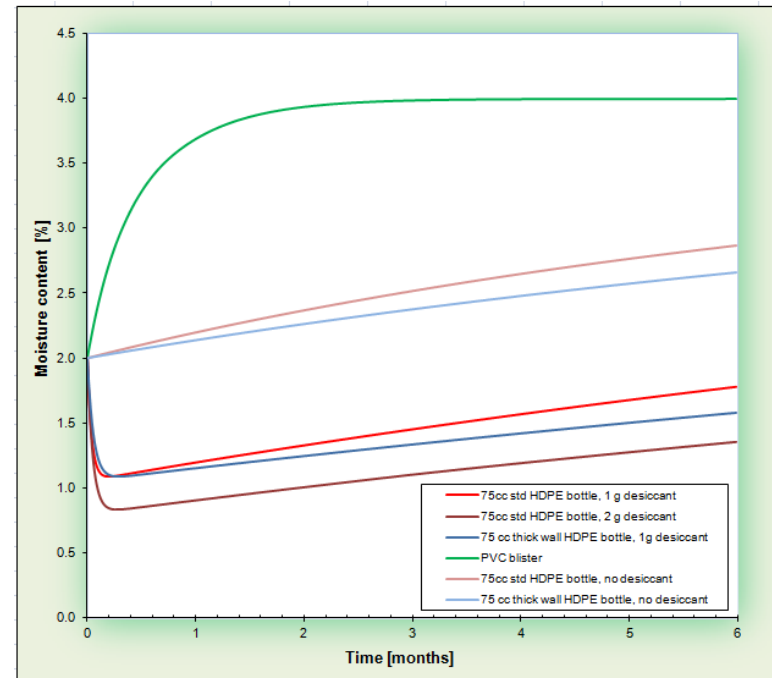
ASAP Case study 3 – Low strength formulation, not common granule, 2015

- Results showed very little degradation
- Unable to model the ASAP data
- However did demonstrate that the product was stable
- Claimed that the new low strength formulation was equivalent to the existing formulations in terms of stability and based the shelf life claim on existing stability data for the higher strength formulations i.e. 24 months
- Submitted to UK, US, France and South Korea and accepted with no regulatory questions
- Subsequent 12 month 25°C/60% RH stability testing showed no significant change from initial



Packaging Examples

- We have used MVTR data for bottles to swap to an equivalent pack post approval, with no supporting stability data in the new bottle but with a commitment to set down annual stability.
- We have used the MVTR per unit dosage form concept to switch between equivalent bottle and tablet count configurations during development, with limited stability data (including changing the desiccant level).
- We have the opportunity to use this concept in a Marketing submission in 2016 to support a longer shelf life claim than the real time stability data would allow.



On going ASAP regulatory strategy

- Include API and formulation ASAP data (for oral solid dosage forms) in Phase I submissions going forward, as supporting information, with the aim of getting regulators used to reviewing ASAP data.
- Identified a possible opportunity for our first ASAP only (no real time stability data) Ph I submission in 2017.
- Throughout development use ASAP data to support changes (eg API route change, minor formulation change), with the aim of reducing the real time stability testing required to support the change and/or claim a longer shelf life.
- First possible opportunity for ASAP data in marketing submission, as supporting information in 2017.
- Started using ASAP data to justify excursions.



Acknowledgements

Nadim Akhtar AZ, UK

Jonathan Bright

Faye Turner

Carolyn Gordon

Andrew Brookes

Arun Kamath

Helen Porter

Steven Mount

Denise Watt

Sarah Hayter

John Nightingale

Magnus Fransson AZ, Sweden

**Thank you
for your attention**



EFPIA TDEG - MAPPs

“CMC Challenges and Opportunities”

- Draft white paper – Dec 2015
- Suggests moving to a reliance on lean stability strategies, stability models and extrapolation for supporting shelf-life
- Specifically mentions ASAP studies

“Accelerated stability studies utilising modelling for predictive stability assessments have the potential to play a key role in the expedited development and delivery of MAPPs projects.....”

“ASAP studies give a greater insight into the stability of a product than traditional stability studies where the focus is on demonstrating stability rather than understanding it.....”

“....it is possible for ASAP studies to be used as the primary source of stability data to predict and assign shelf lives and retest periods, utilising limited long term traditional stability data as supportive data to verify the model over a shorter timeframe. This would significantly reduce the time for development”

