Applications of ASAP in the Generics Industry

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Why ASAP?

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What Does ASAP Do?

- Science based and data driven approach for shelf life prediction
- Predict shelf life within weeks instead of months
- Experiments can be flexible compared to fixed ICH conditions
- Evaluation of formulation options
- Provide rationale for packaging design & optimization
- Stability data generated using ASAP has been accepted by regulatory agencies for IND filings with commitments for long term data

Goal

- To use this approach as a development tool that considers both chemistry and packaging aspects to ensure shelf life expiry for new products

Actual Applications of ASAP

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- Formulation Development – Screening/Selection
- Specification Setting – Development
- Degradant Investigations (Development/Lifecycle)
- Manufacturing Process changes (e.g. Zanchetta to Fluid Bed)
- Raw Material Changes (API or critical excipients)
- Evaluation of API Process Changes on DP stability
- Packaging Selection/Optimization

What is ASAP?

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Accelerated Stability Assessment Program (ASAP) is an alternative approach for accelerated prediction of drug expiry.

Modified Arrhenius Equation:

$$\ln k = \ln A - Ea/RT + B(\%RH)$$

Experimental considerations: independently varying T and %RH to achieve "iso-conversion" under stress conditions

Iso-conversion: The end point of the stress studies is to achieve fixed amount of degradation (i.e. SPECIFICATION LIMIT) instead of a fixed time duration

Case Study – 1(Tablets)

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Background:

API manufacturer notified the site of changes in the micronization step for the Drug Substance and that out of trend stability results were obtained for the primary degradant.

Impact:

Multiple Drug Product Batches had already been manufactured utilizing new process API prior to notification from the API supplier.

Challenge/Questions:

Can ASAP be used to predict the stability results faster than the accelerated stability data (i.e. 3 months 40°C/75 %RH)?

Background information on the Formulation

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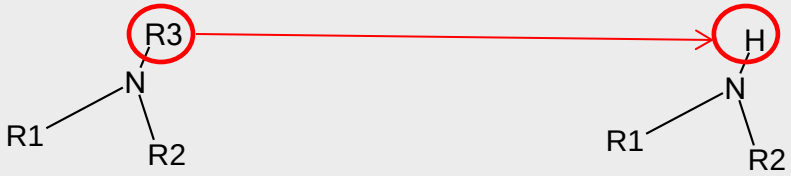
Formulation	Mfg Process	Packaging
API	Dispense	30 Count
Lactose Monohydrate	Blend	90 cc HDPE HIS Bottle
Mannitol	Wet Granulation (High Sheer)	Dessicant Silica Gel(1g)
Starch	FB Drying	PP Closure
Crospovidone	Comil	
Mg Stearate	Blend	
Buffer System	Tablet Compression	

The Critical Relative Humidity (CRH) values for the excipients and API were considered in the construction of the design space and conditions above the lowest CRH were generally avoided

Chemistry of the Degradant



N-Dealkylation of the parent compound was observed during Forced Degradation studies (oxidative and heat stressing conditions)

Degradant Specification		
	Release	Stability
Drug Substance	NMT 0.15%	NMT 0.15%
Drug Product	NMT 0.2%	NMT 0.3%
Tablet Shelf Life = 18 months		

Experimental Considerations and Design

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- Two different lots of Tablets and API were analyzed, one each from the pre and post micronization process change

Temperature (°C)	%RH	Salt	Time Points (Days)
50	50	NaBr	5, 10, 17
60	30	$MgCl_2$	10, 17
70	11	LiCl	5, 10, 17
70	75	NaCl	5, 10
80	30	$MgCl_2$	7, 17
80*	50	NaBr	6, 13
5*	N/A	N/A	17

* 2 Replicates

- Conducted as a reverse stability study such that all samples were removed from their respective stability chamber and prepared and analyzed on the same day in order to eliminate day-to-day variability.

Equipment Summary

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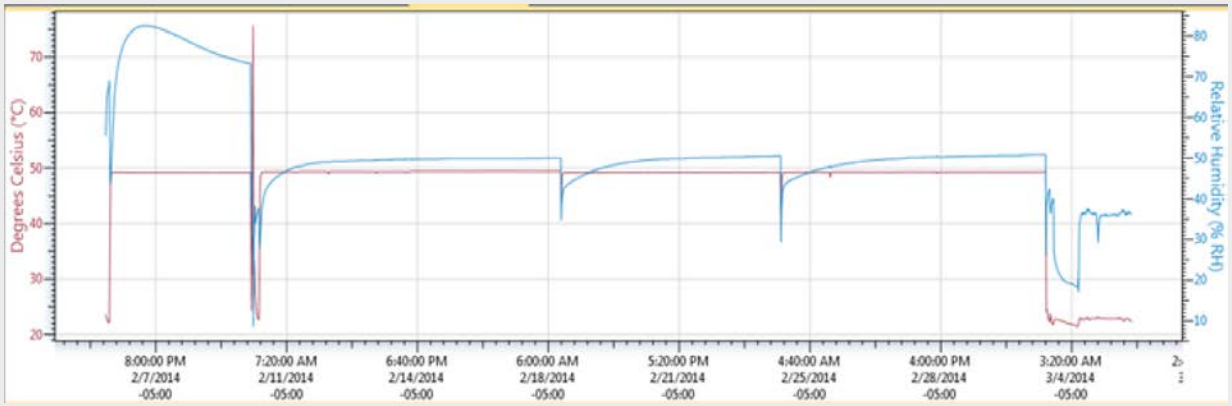
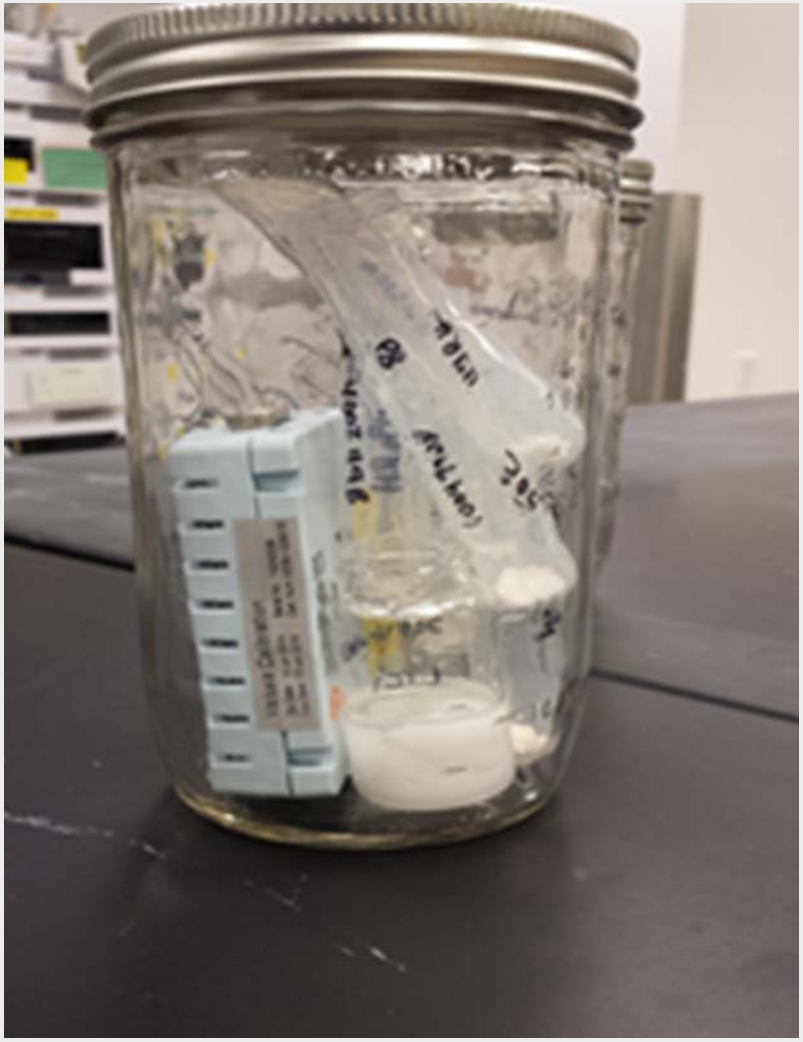
High Tech Humidity Chambers

Ovens



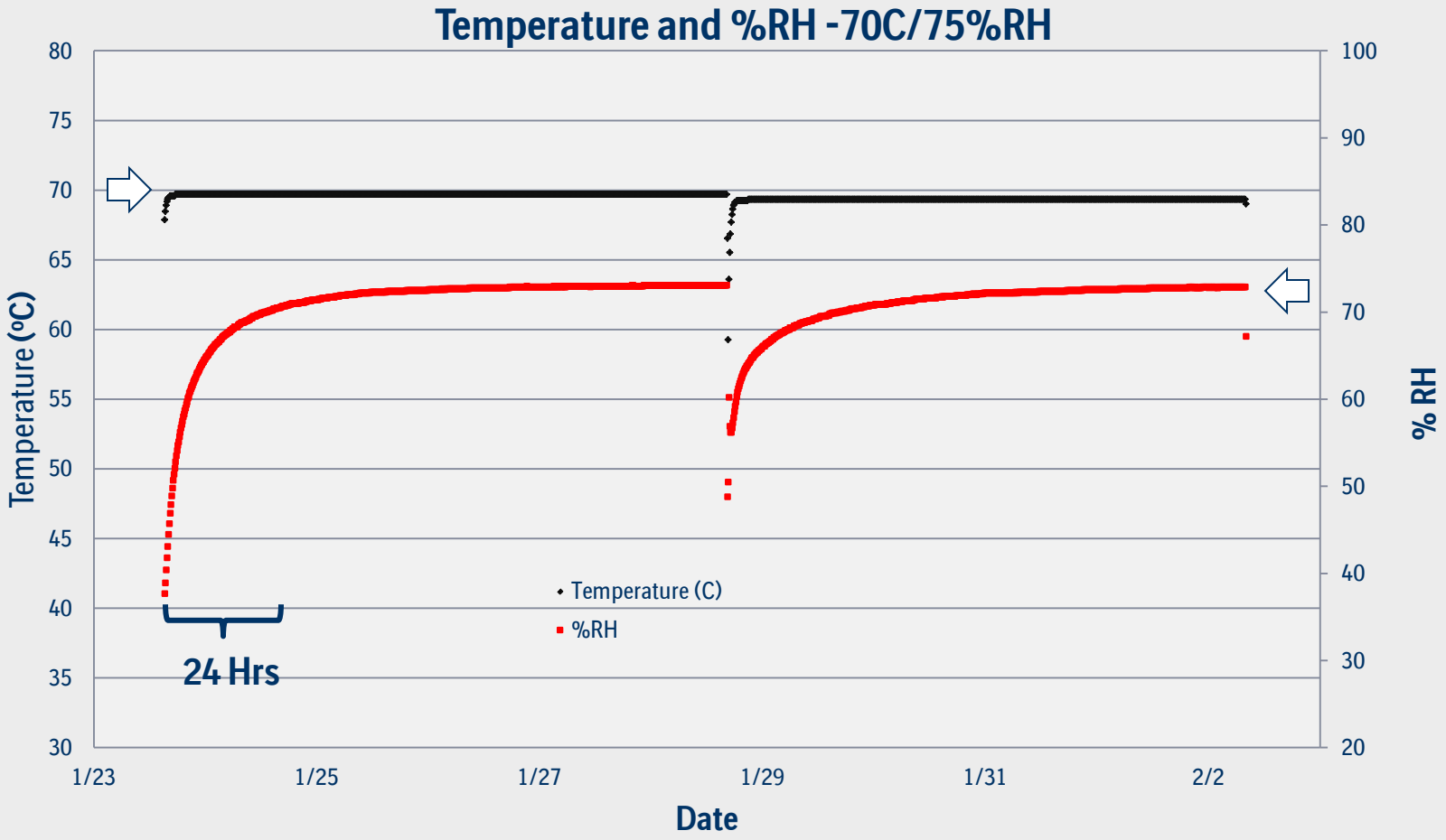
Equipment Summary…



Advantage:
Run Multiple Humidity conditions and Studies concurrently

ASAPprime®
better decisions faster

T and % RH behavior in High Tech Chambers…



Temperature and Relative Humidity Summary

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Nominal Condition (°C/% RH)	Mean Temperature (°C)	% RSD	Mean %Relative Humidity	% RSD
50/50	47.9	4.2	50.6	6.3
60/30	58.0	2.4	30.4	4.3
70/11	69.5	1.0	11.0	3.6
70/75	69.5	0.6	70.9	5.8
80/30	81.3	1.0	24.8	3.2
80/50	81.0	0.4	49.0	2.2

Measured Levels of the Degradant

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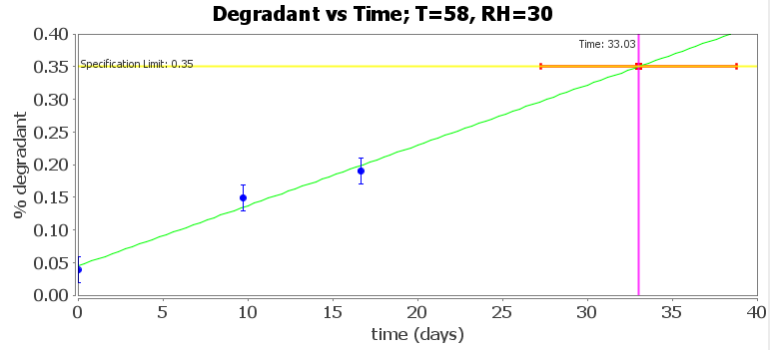
Time (days)	Temp. (°C)	%RH	DP Pre Change	DP Post Change	API Pre Change	API Post Change
			Degradant (% w/w)			
Control	5	NA	0.189	0.040	0.054	0.093
Control			0.181	0.037	0.049	0.088
4.6	47.9	50.6	0.232	0.081	0.065	0.102
9.7			0.259	0.104	0.066	0.121
16.6			0.299	0.139	0.082	0.165
9.7	58.0	30.4	0.280	0.149	0.080	0.158
16.6			0.313	0.190	0.088	0.190
4.7	69.5	11.0	0.283	0.159	0.082	0.197
9.7			0.338	0.208	0.079	0.214
16.6			0.409	0.261	0.101	0.254
4.6	69.5	70.9	0.534	0.483	0.090	0.209
9.7			0.776	0.788	0.091	0.233
6.7	81.3	24.8	0.551	0.460	0.108	0.219
16.6			0.707	0.595	0.155	0.355
5.7	81.0	49.6	0.748	0.718	0.103	0.242
12.8			0.883	0.793	0.113	0.244
12.8			0.888	0.848	0.106	0.284

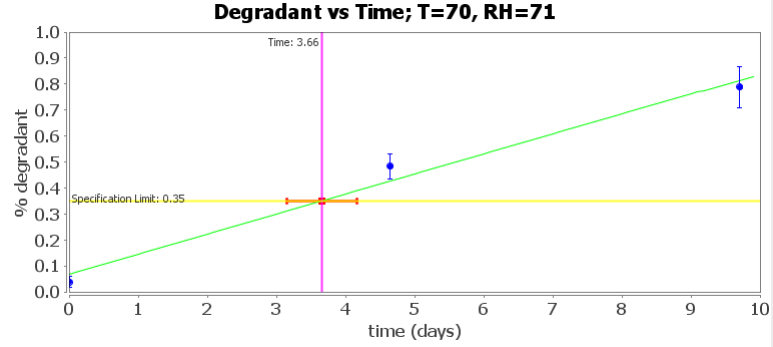
Replicate Preparations Show good Agreement

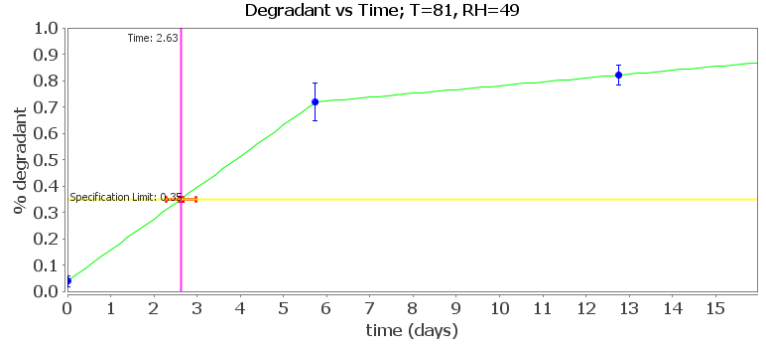
Results show good range – from QL to ~2xSpec limits

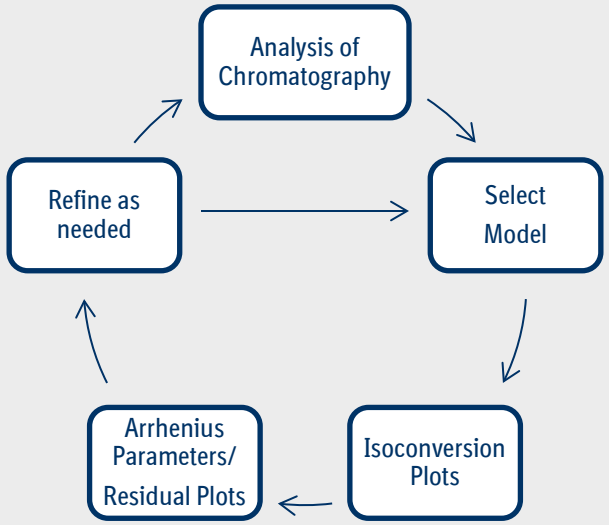
Degradant growth in API & DP ≥ the Spec limit

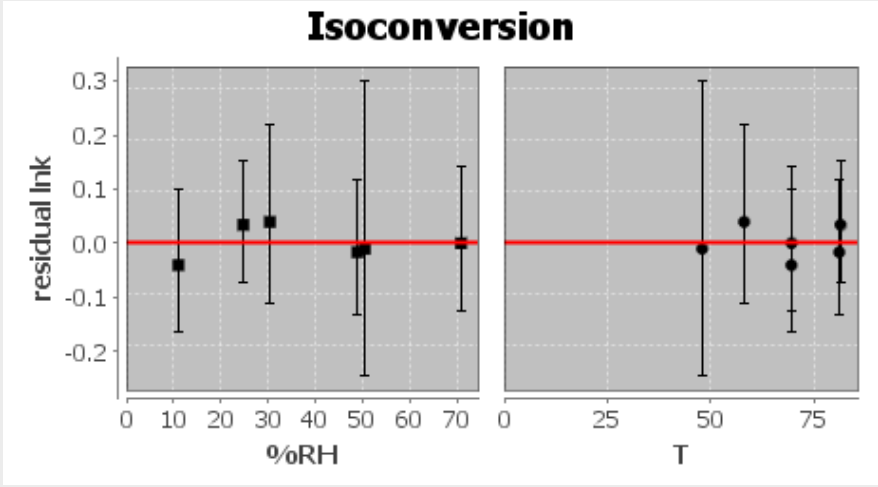
Evaluation of ASAP Data







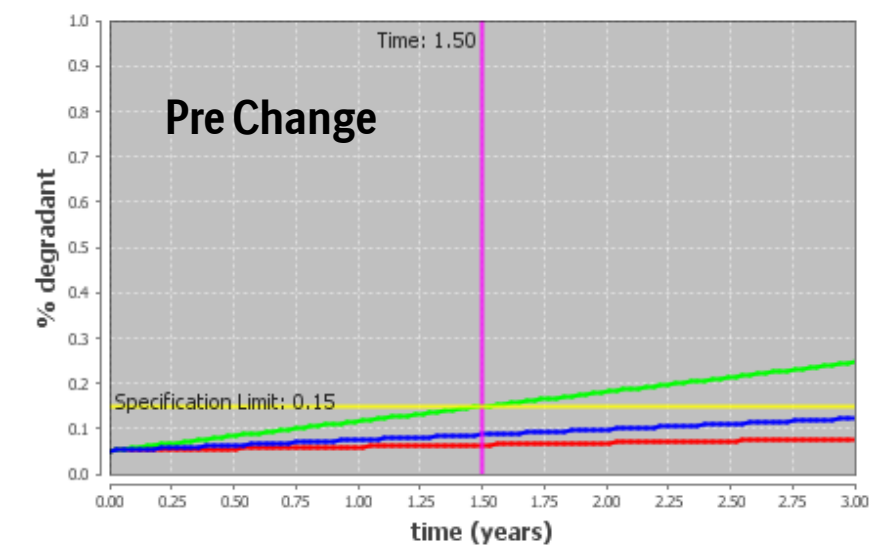


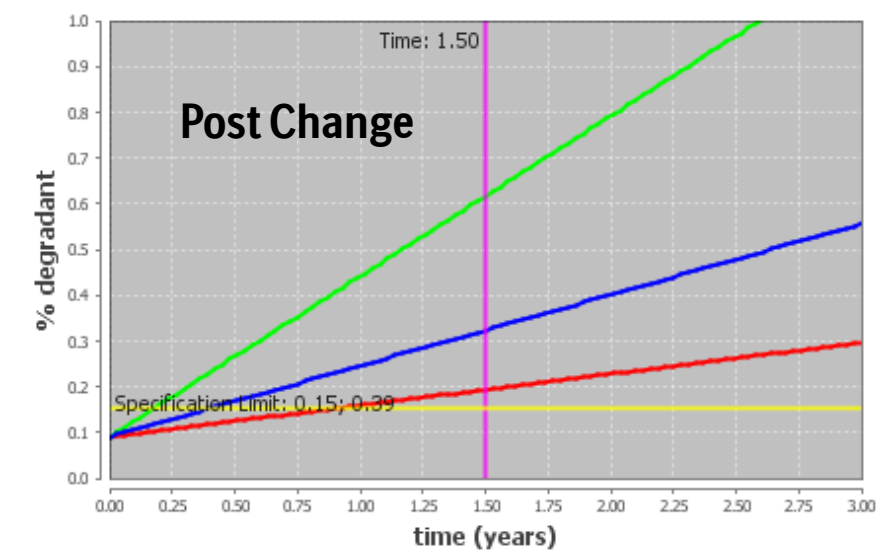


Residuals Plot – small and evenly distributed around zero

API Results – Primary Degradant (Diffusional Model)

API Batch	Ln A	E_a (kcal/mol)	B	R^2
Pre Change	16.4 ± 6.1	15.5 ± 4.2	0.002 ± 0.012	0.91
Post Change	24.5 ± 2.9	19.3 ± 3.8	0.005 ± 0.012	0.94





- The rate of formation for the primary degradant from the new micronization process is much faster than the rate of the old micronization process
- Observation is consistent with hypothesis that this material has a higher level of amorphous content due to more intense milling conditions

Model Evaluation (Fitting) using ASAP Prime – Drug Product

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Fit Parameter	Fit Model				
	Default	Zero Order	First Order	Second Order	Diffusion
lnA	25.8 ± 2.8	22.7 ± 2.8	22.8 ± 2.9	22.9 ± 3.0	42.6± 5.1
E_a	20.7 ± 1.9	18.7 ± 1.9	18.7 ± 2.0	18.8 ± 2.0	32.6 ± 3.5
B	0.029 ± 0.003	0.030 ± 0.003	0.030 ± 0.003	0.030 ± 0.003	0.046 ± 0.006
R^2	0.999	0.993	0.993	0.993	0.995
Probability of Passing at 1.5 yrs	91	73	72	73	100
Shelf life Prediction (Yrs)	2.44	1.88	1.89	1.89	No Limit

Selected Model
(R^2, Isoconversion plots, Residual Plots)

Drug Product Results (Primary Degradant)

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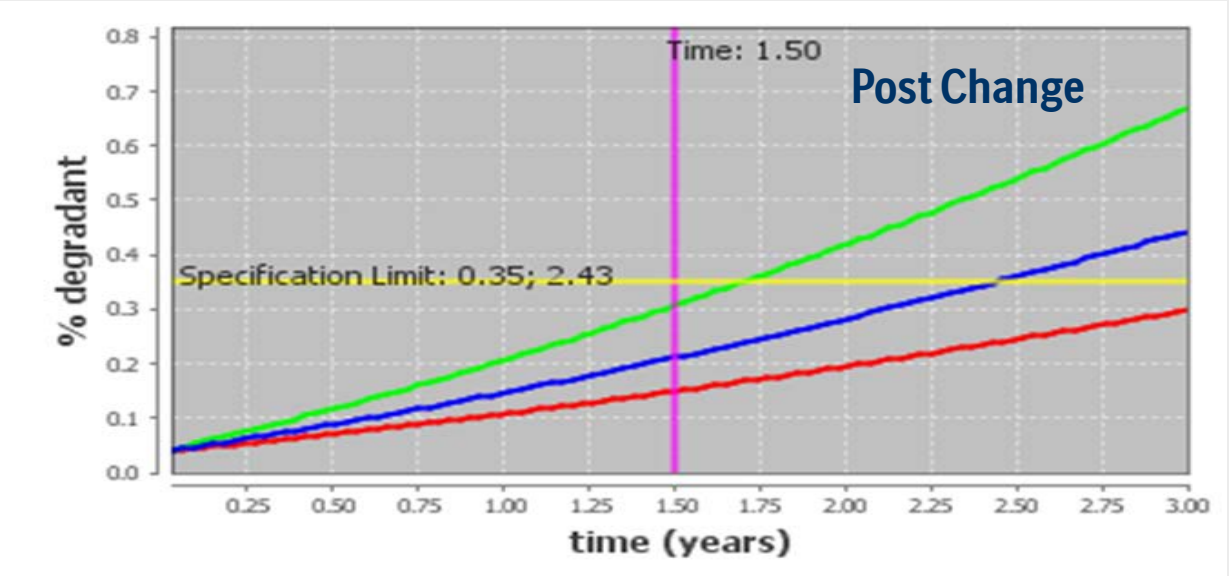
DP Batch	Ln A	Ea (kcal/mol)	B	R^2
Pre Change	23.4 ± 3.0	19.0 ± 2.1	0.027 ± 0.004	0.995
Post Change	25.8 ± 2.9	20.7 ± 3.0	0.029 ± 0.003	0.999

- The two batches were found to be statistically equivalent as the values for lnA, Ea and B fall within the corresponding confidence intervals between the two batches
- Overall fit of the data obtained R^2 values $\geq$0.995…I mean come on people…that's AWESOME!



ASAP – used to set Alert Limits for DP release

- Due to the potential formation of high levels of the degradant there was a need to control the amount of the degradant present in the API utilized for production of the Drug Product
- Utilized the ASAP data to predict the shelf life for different degradant levels at release of the Drug Product

Initial Degradant Level (%)	Mean Predicted Shelf-life (Yrs)	Probability of passing at 18 months
0.0	2.8	95.4
0.05	2.5	92.7
0.10	2.2	86.4
0.15	1.8	69.4

Alert limit for DP - determined

Alternate Packaging Evaluation – can the shelf life be improved?

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- Current packaging configuration for the Tablets is 90Ccc HDPE bottles with 1 gram of silica gel desiccant

Packaging	Silica Gel (g)	Mean Predicted Shelf Life (yrs)	Probability of passing at 18 Mo	Probability of passing at 24 Mo
90 cc 0.02" HDPE bottles HIS, 30 Tablets	0	0.9	16.7	6.1
	1	2.3	85.9	63.7
	2	3.0	94.8	83.8

- Amount of desiccant is critical to the shelf-life of this product and the current packaging configuration could benefit from utilizing an additional one gram of desiccant based on the predicted shelf-life improvement

Comparison of ASAP predicted stability results vs actual

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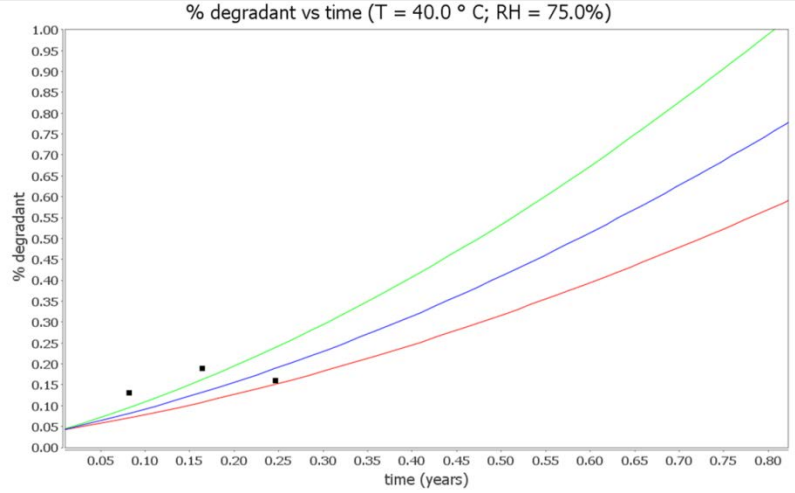
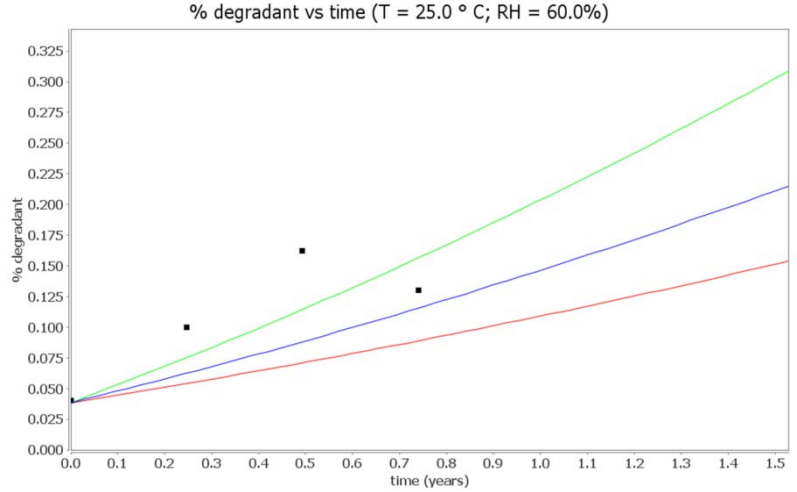
Accelerated Stability (40/75)
data available at 0, 1, 2, & 3 months

Long Term stability (25/60)
data available at 0, 3, 6, & 9 months





Good agreement between the ASAP prediction interval and the actual stability results at both conditions!!

Summary - Case Study 1

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The API produced with the new milling process showed an increased rate of degradant formation – related to increased amorphous content

Control Strategy – established an alert limit for the degradant at Drug Product release (alert limit set to NMT 0.10% to ensure shelf-life)

The rate of formation for the Degradant was found to be statistically identical for both drug product batches

The batches are predicted to have shelf lives greater than 18 months based on the rate of degradant formation – consistent with approved shelf life

ASAP results accurately predicted the 3 month accelerated results!

Case Study – 2 (Tablets)

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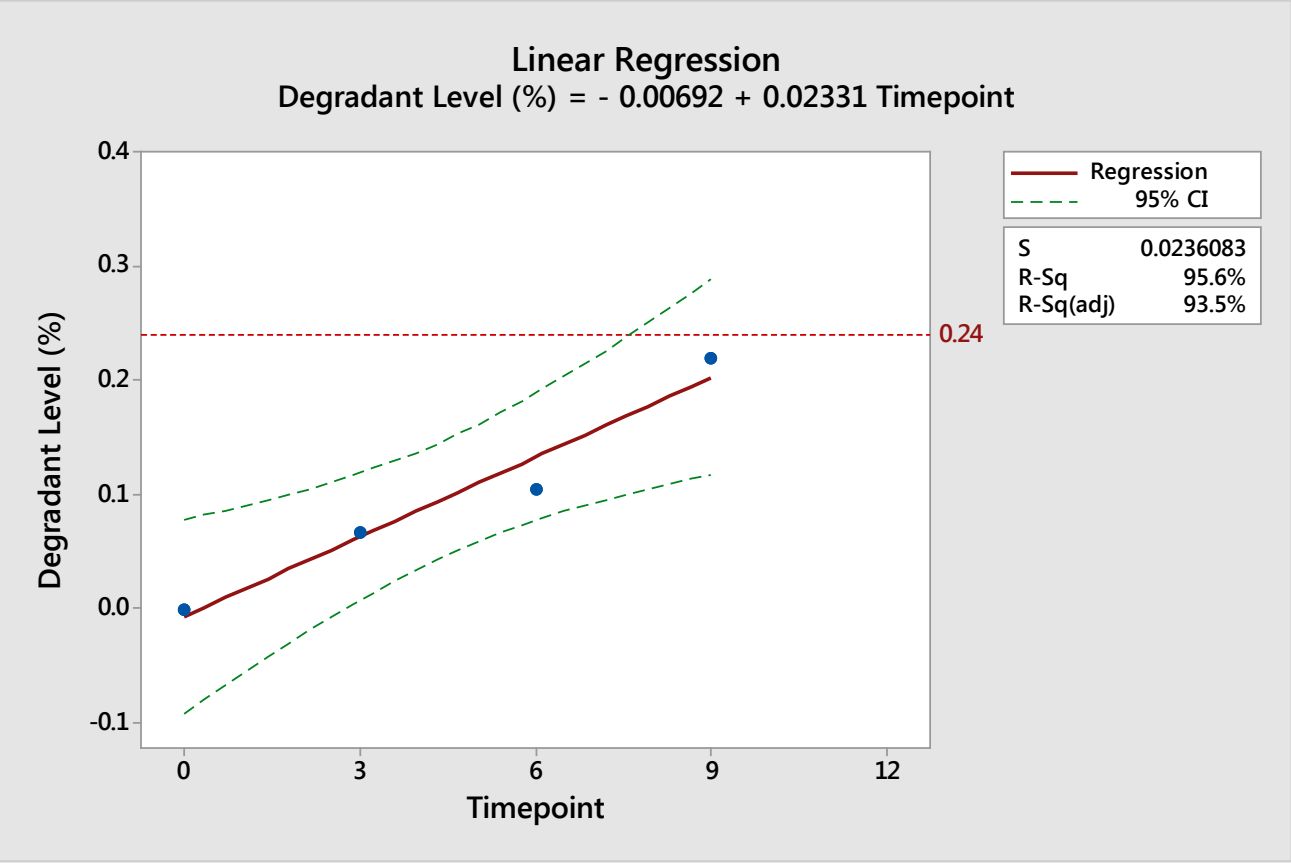
Background:

- Stability testing at 9 months - OOT result for Specified Unknown Degradant in PVC Blisters
- Trending predicted OOS at 12 months – approved shelf life 24 months

Investigation Team - Goals:

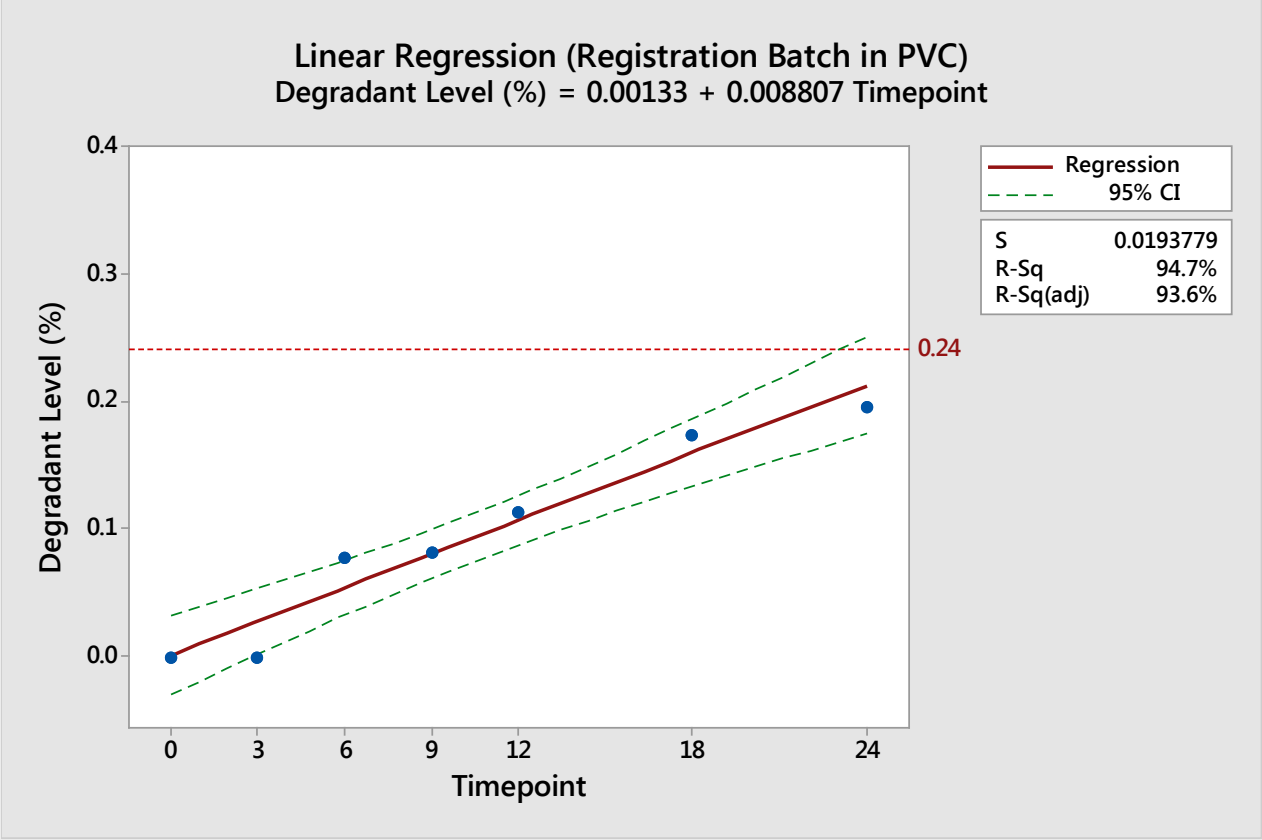
- Identify the specified (unknown) degradant
- Understand mechanism of degradant formation
- Perform a Medical Evaluation, possibly file for limit change (NMT 0.2%)
- Identify potential control measures, process improvements, product component improvements, **packaging changes** to improve stability

Specified Unknown in PVC Blisters – OOT Batch



Stability Specification Limit = NMT 0.2%
Batch Predicted to be OOS by 11 Months
(95% CI = 8 months)

Stability of Registration Batch in PVC Blisters



Mean Predicted Stability ~ 28 months
95% CI = 23 months

Comparison to Stability results from Registration Batches

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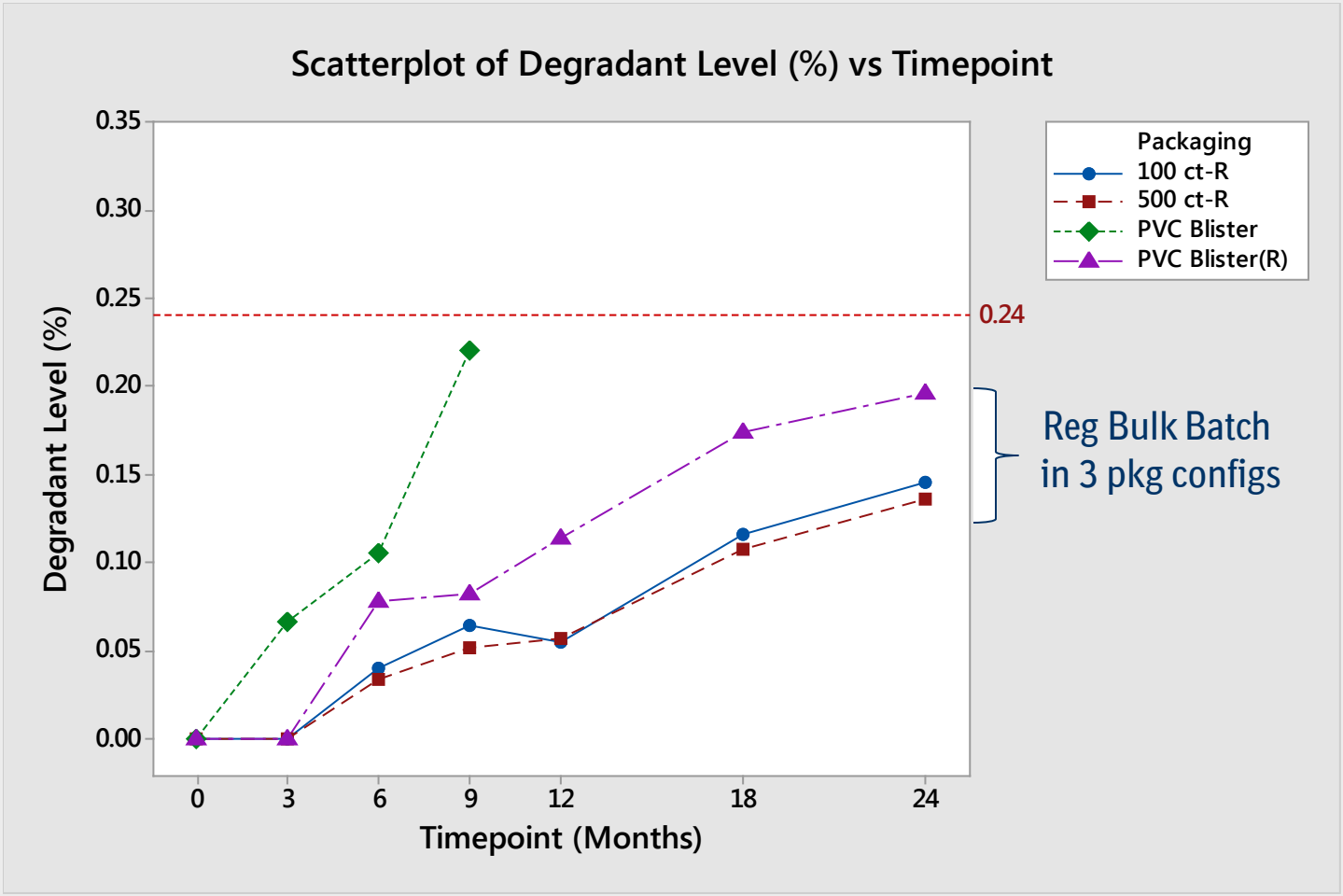

Degradant Rate Formation in PVC Blister- Faster

Potential Contribution Factors…

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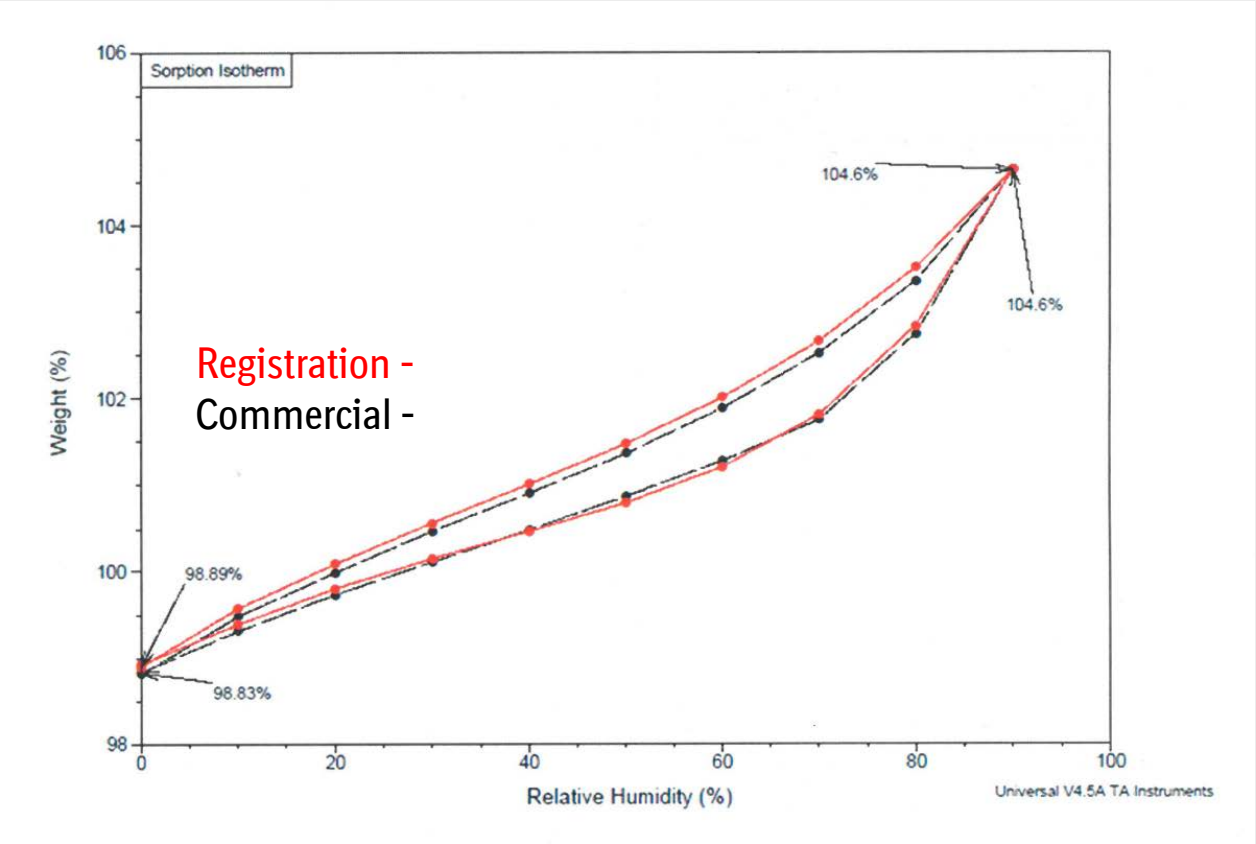
- Is process variability/ hence batch to batch variability a a potential factor?
- Were there significant Equipment/Process changes made since Registration?
- Changes in Tablet properties, water content or sorption profile?
- Was API degradation a contribution factor?
- What is the Maximum level of degradant?
- Could we modify the Packaging to reduce moisture ingress?
    - Replace PVC Blisters?
    - Change Bottles to Thick walled?

Proposed to conduct an ASAP study in order to address most of these questions!

Comparison of Moisture Sorption



DVS (water sorption/desorption) compares well with the Registration batch to the batch that was trending out on Stability

Experimental Design

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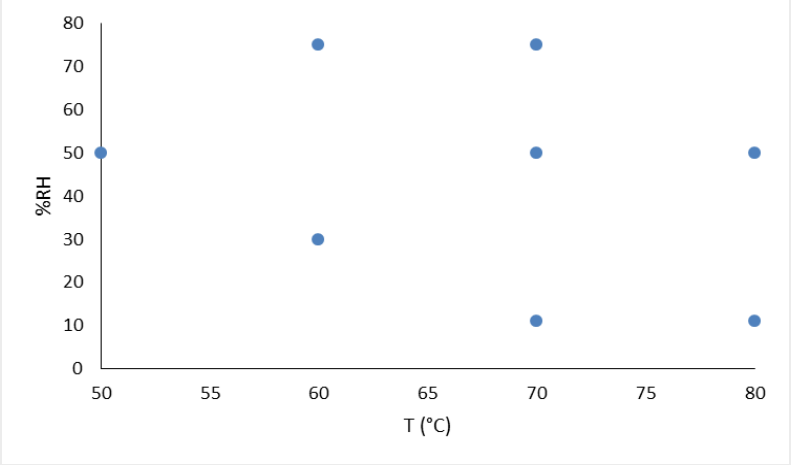
T (°C)	%RH	Salt	Time points	Number of analyses
50	50	NaBr	7, 14, 21	3
60	30	$MgCl_2$	7, 14, 21	3
60	75	NaCl	4, 14, 21	3
70	11	LiCl	7, 14, 21	3
70	50	NaBr	6, 14, 21	3
70	75	NaCl	2, 7, 14	3
80	11	LiCl	5, 14, 21	3
80	50	NaBr	3, 10 (2 repeats), 21	4
5	--		21 (2 repeats)	2
TOTAL				27

Two Batches of DP
One Lot of API
Temperature range: 50-80 °C
Relative Humidity: 11-75%
Multiple conditions with cross-overs on Temp and % RH

Overall > 90 Samples prepared and Analyzed

Graphical representation of the ASAP experimental design



General Chemistry of the Degradant – Aldol Chemistry

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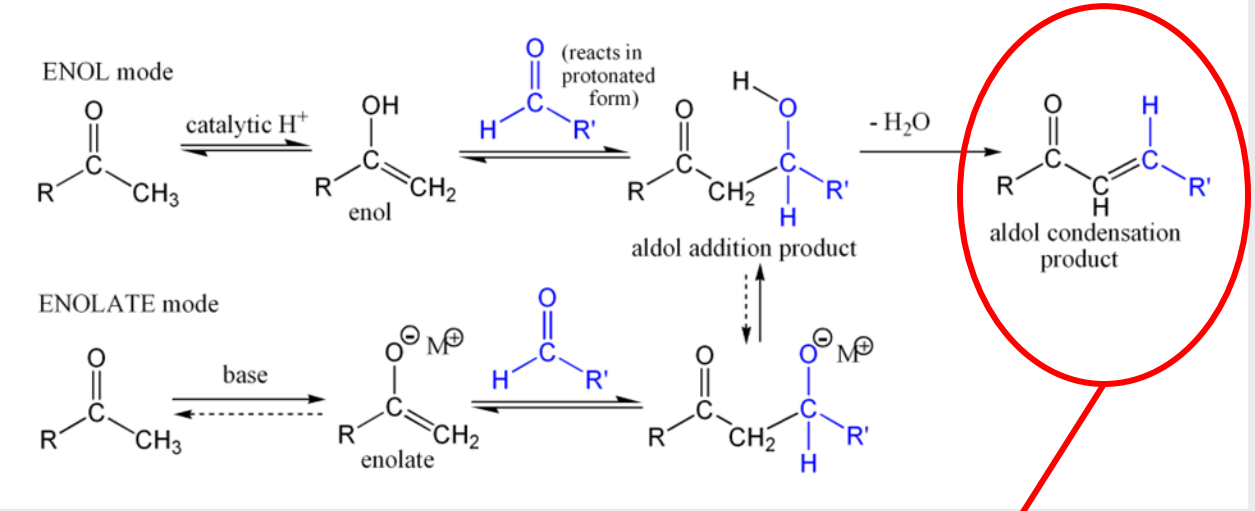
Structure of the Unknown = Dimer (Aldol Addition Product)

Aldol Addition Product formation is sensitive to pH and Temperature

Tablet pH ~6.6



Hypothesis:
If equilibrium chemistry is at play we could expect the dimer levels to stabilize (plateau)

No evidence for Aldol Condensation Product from extensive MS Studies

ASAP Experimental Results…

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Analyzed in a single run using the DP Release method

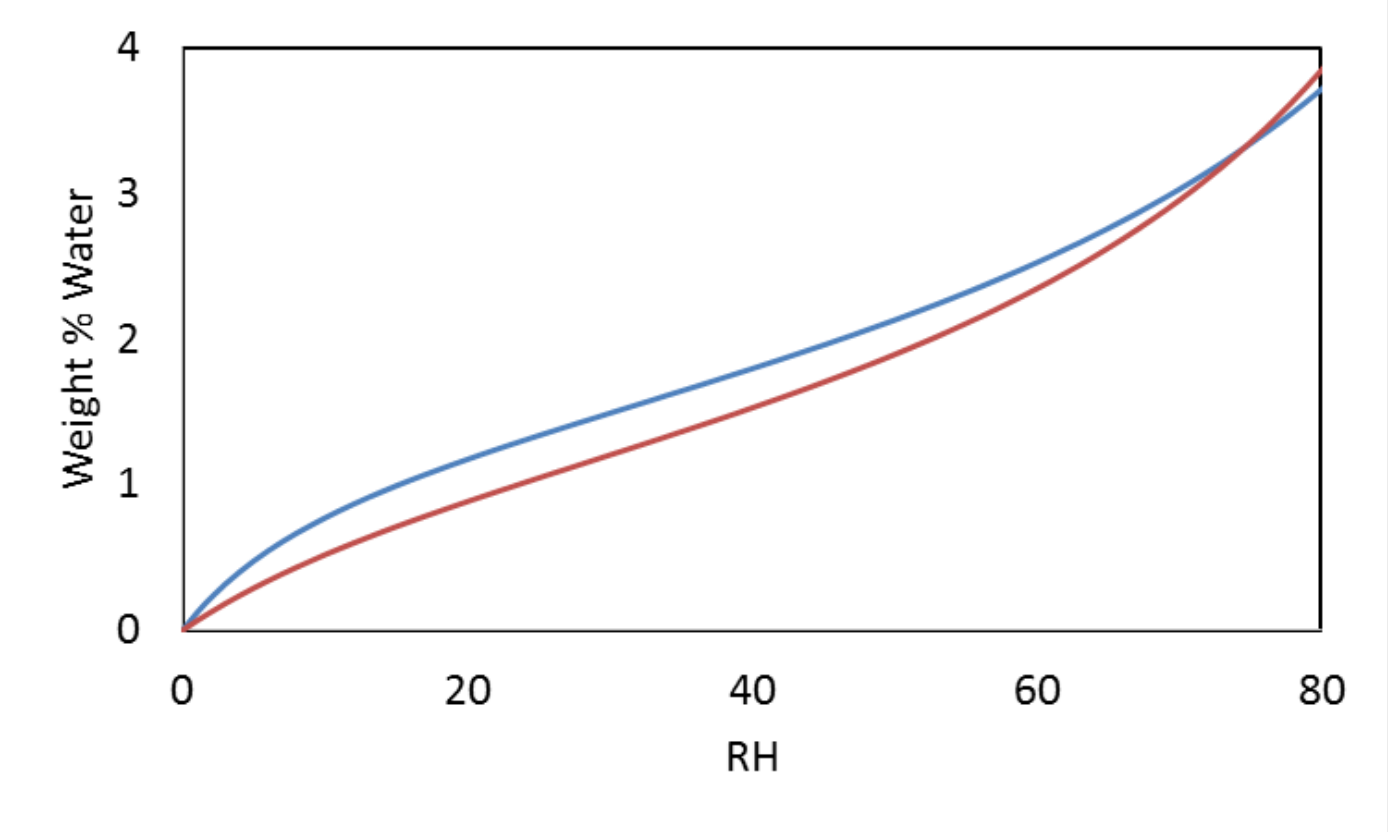
(minimize variability)

Time (days)	Temp. (°C)	%RH	Lot A	Lot B	API
control	---	---	0.018	0.017	ND
7	49.3	49	0.066	0.071	0.014
13			0.093	0.092	0.010
21			0.107	0.102	0.012
7	59.8	30.6	0.056	0.061	0.011
13			0.072	0.081	0.013
21			0.095	0.103	0.008
4	59.4	73.8	0.121	0.126	0.010
13			0.220	0.218	0.016
21			0.236	0.244	NA
7	66.1	15.3	0.051	0.057	0.011
13			0.078	0.080	0.012
21			0.096	0.101	0.011
6	65.9	52.1	0.094	0.096	0.013
13			0.137	0.155	0.012
21			0.191	0.202	0.008
3	66.7	73.2	0.131	0.130	0.013
7			0.176	0.194	0.009
13			0.215	0.216	0.009
5	77.9	15.5	0.068	0.067	0.013
13			0.123	0.130	0.011
21			0.191	0.206	0.009
3	78.4	51.7	0.095	0.104	0.011
10			0.193	0.191	0.011
10			0.191	0.185	0.011
21			0.249	0.255	0.009

API – No detectable change in the dimer levels

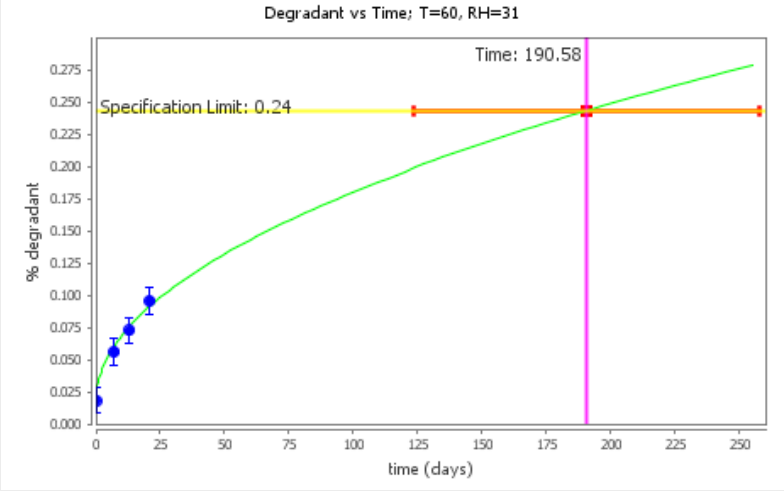
Both DP Batches showed very comparable results – maximum level of the dimer ~0.25% under the most extreme conditions

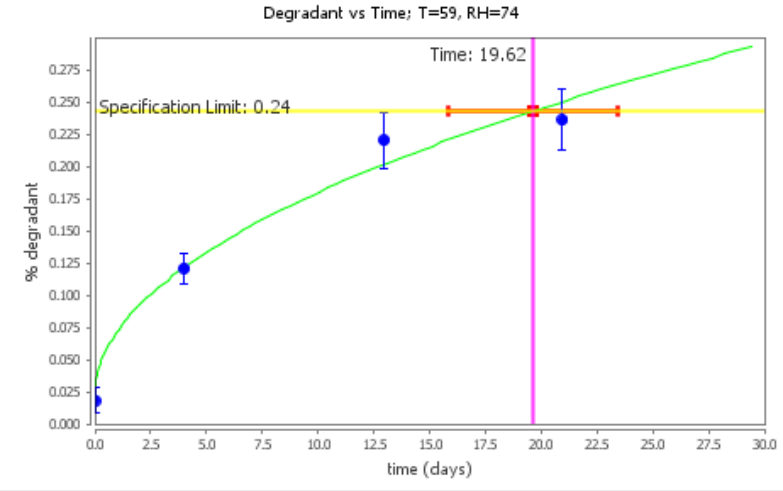
Calculated Moisture Isotherm



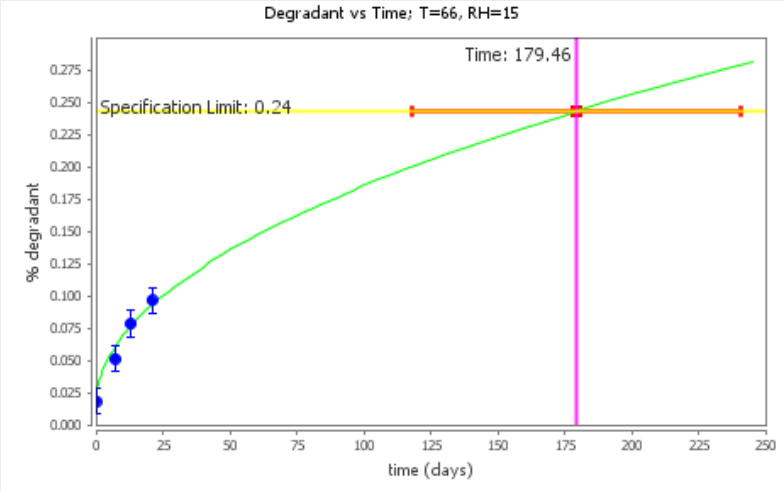
Moisture sorption isotherm calculated using the ASAPprime® software (blue curve) and measured by BI (red curve).

Evaluation of ASAP Data
Degradant Fit Plots and Residual Plot





Low Relative Humidity



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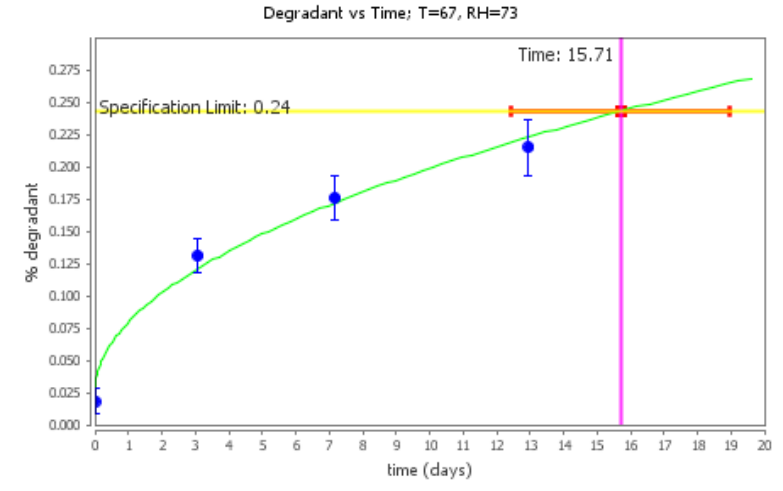
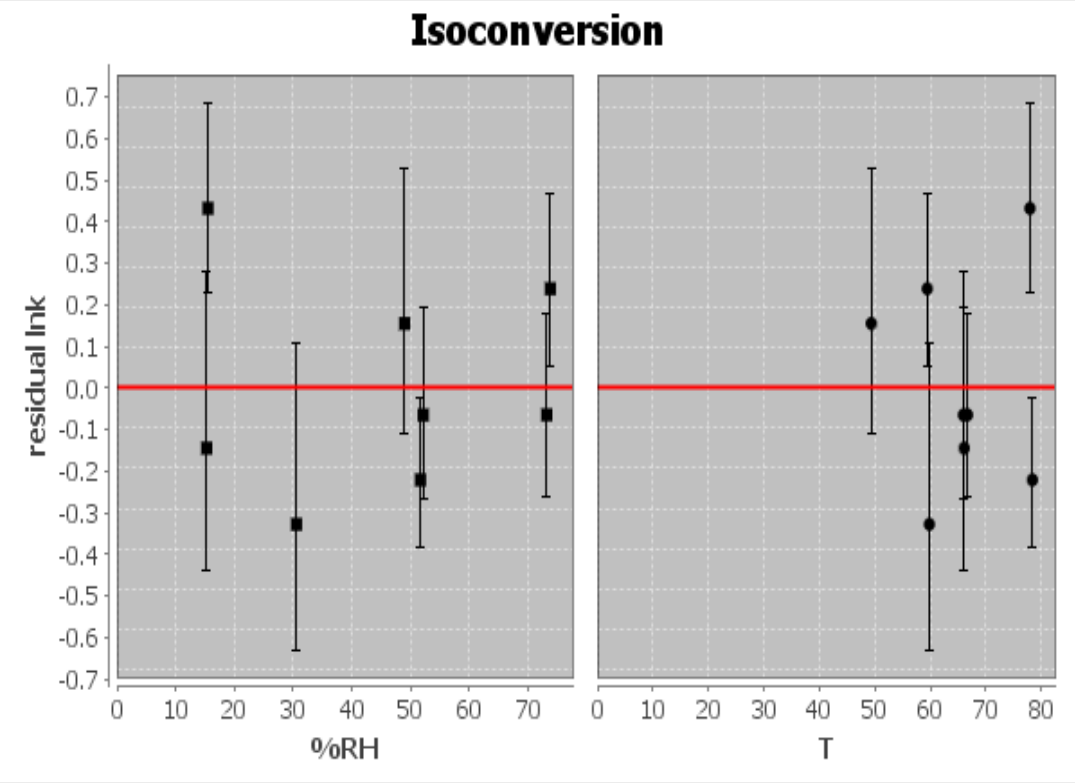


Evaluation of ASAP Data
Degradant Fit Plots and Residual Plot



Residuals Plot – small and evenly distributed around zero

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Summary of the ASAP*prime*® fitting results (Diffusional Model)

DP Batch	Ln A	Ea (kcal/mol)	B	R^2
A	18.0 ± 6.0	16.8 ± 4.2	0.040 ± 0.008	0.939
B	18.8 ± 5.9	17.2 ± 4.1	0.039 ± 0.007	0.945

Several observations were made based on the data fitting:

- The two lots of drug product are statistically identical
- The dimer shows a relatively low activation energy (17 kcal/mol compared to the average drug product having an activation energy of 29 kcal/mol)
- The dimer formation has a moisture sensitivity that is similar to the average drug product (B factor of 0.04)

Packaging Evaluation (bottle modification, dessicant(Silica Gel), alternate blister materials)

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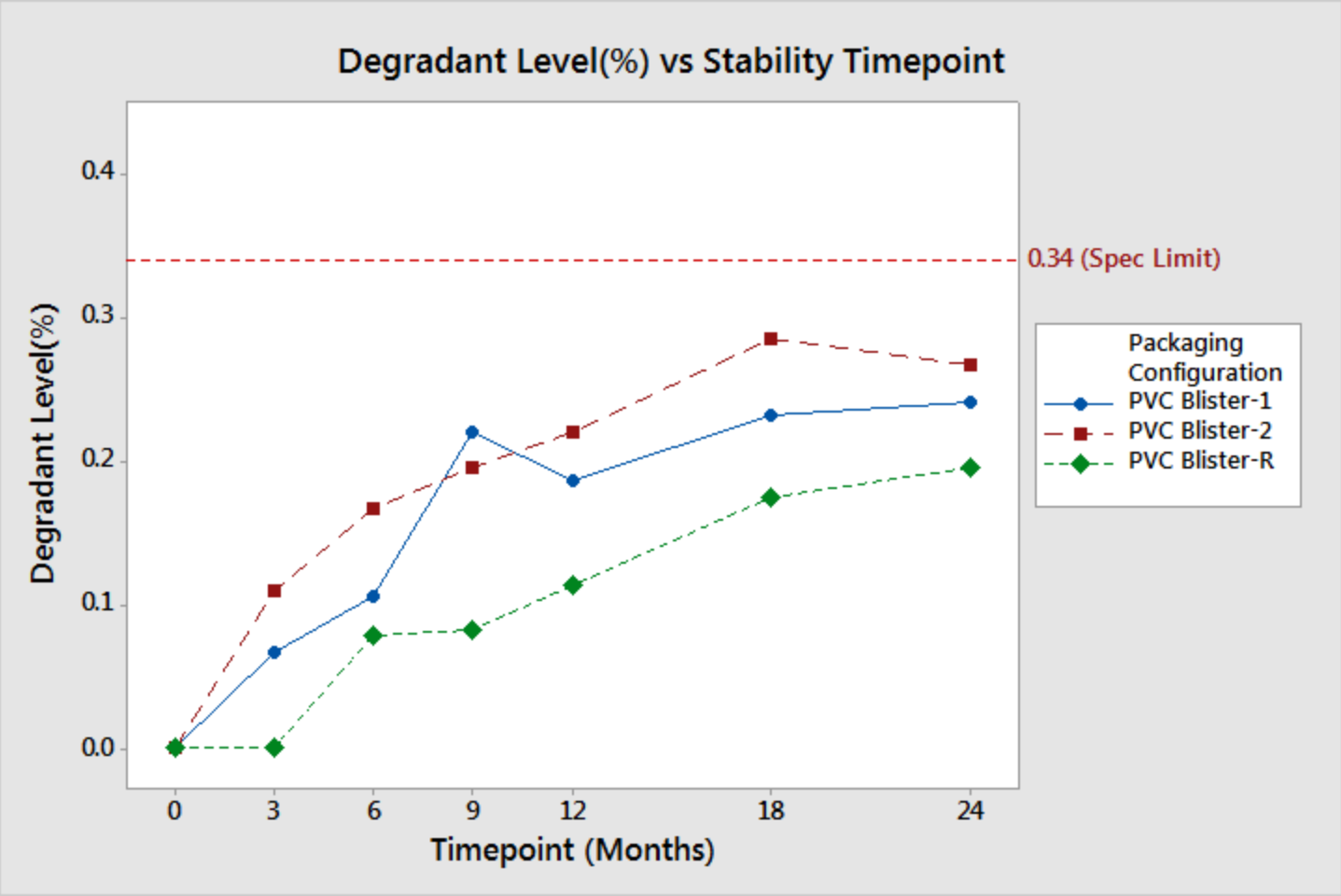
Packaging	Desiccant (g)	Mean Shelf-life predicted	Probability of passing at 2 yrs
150-cc 0.02" HDPE bottles; HIS	0	>5 yrs	96.50%
	0.5	>5 yrs	97.40%
	1	>5 yrs	98.00%
150-cc 0.04" HDPE bottles; HIS	0	>5 yrs	96.90%
	0.5	>5 yrs	97.70%
	1	>5 yrs	98.20%
PVC blister	----	>5 yrs	85.50%
PVDC blister	----	>5 yrs	88.20%
Aclar RX160	----	>5 yrs	90.60%
Aclar Ultrx 2000	----	>5 yrs	94.20%
Aclar Ultrx 3000	----	>5 yrs	94.90%
Aclar Ultrx 4000	----	>5 yrs	95.20%
Aclar Ultrx 6000	----	>5 yrs	96.20%
Foil-foil blister	----	>5 yrs	97.10%

Current Packaging was found to be sufficient for 2 yr shelf life, therefore additional cost with packaging modifications were not justified

Long Term Stability Results PVC Blisters



Long Term Stability Results – All Packaging Configurations

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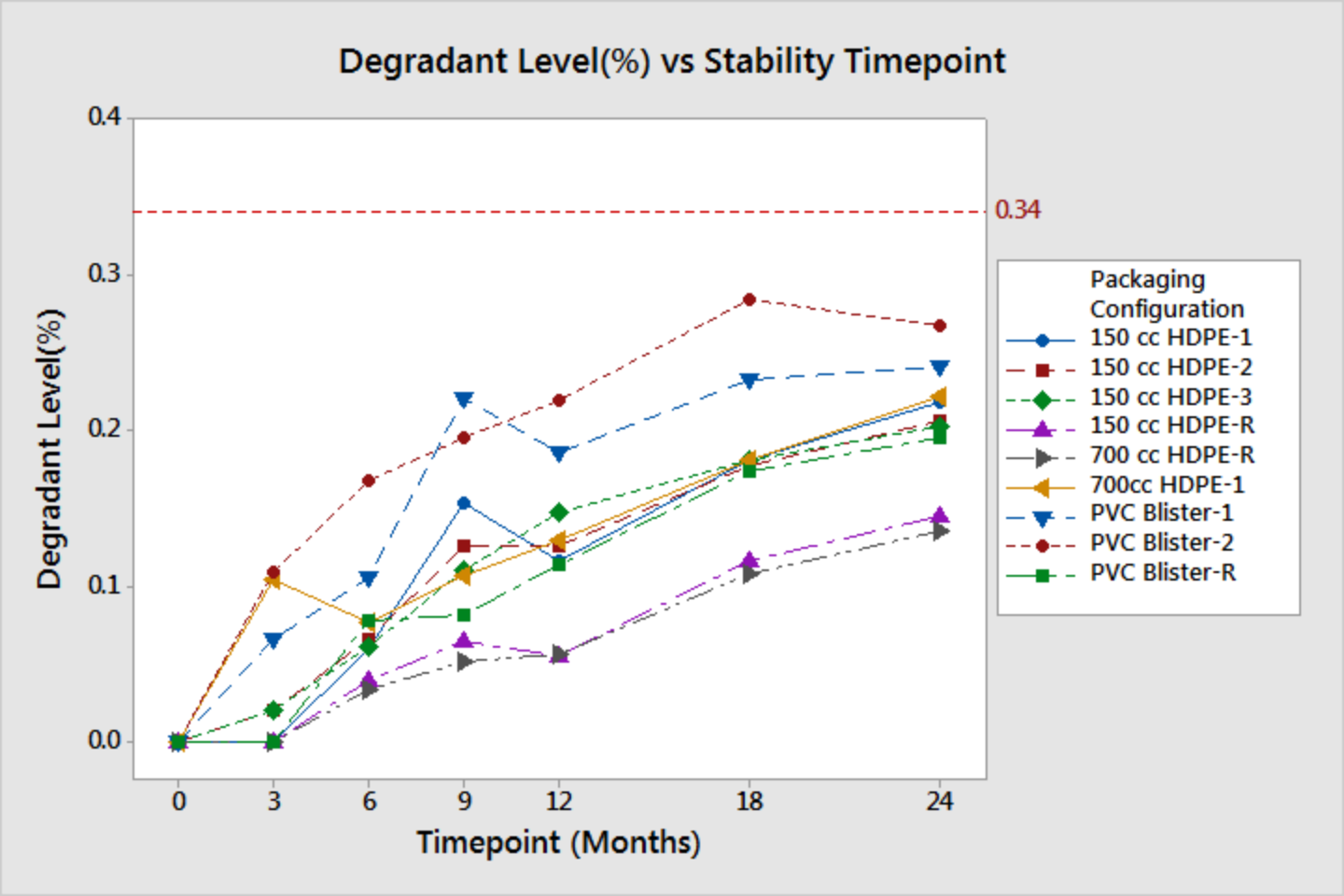

Summary

- The DP two lots were found to be statistically identical for the Dimer.
- For bottles, two-year shelf-life (25°C/60%RH) in thin-walled (2 mil) bottles should not require desiccant.
- No additional gains in in shelf life by moving to thick walled bottles
- For blister packaging, PVC is acceptable, no additional gains in shelf life by moving to alternate packaging
- Additional stability studies to investigate alternate packaging configurations were cancelled

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Case Study 1	Case Study 2
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Questions?