



ASAP for parenteral formulation development – solutions and lyophilisates

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 **NOVARTIS** | Reimagining Medicine

Agenda

- **Parenteral, topical and ophthalmic formulation in Novartis**
- What is ASAP?
- Liquid formulation development:
 - 2 Quick development of sensitive compound for organic concentrate formulation
 - Prediction vs real time when drug substance change?
- Lyophilisate formulation development –
from unstable liquid formulation to stable lyophilisate using ASAP and/or DoE

ParTop & Ophtha Dosage Forms and Projects



Parenteral delivery systems

- liquid and freeze dried products
- liposomes, nanoparticle, active and passive targeting

Parenteral depot systems

- microparticle, implants, in situ gelling systems
- Microcrystal suspensions

Convenient topical applications

- ointments, gels, creams, foams

Transdermal therapeutic systems

- patches, microneedles

Ophthalmic dosage forms

- Ophthalmic solution and suspension in drop container, gels, semi-solids, device

Types of parenteral formulation developed at Novartis using ASAP

1. Liquid in vials
2. Lyophilisate in vials
3. Liposomes and mixed micelles
4. Gel and cream

Agenda

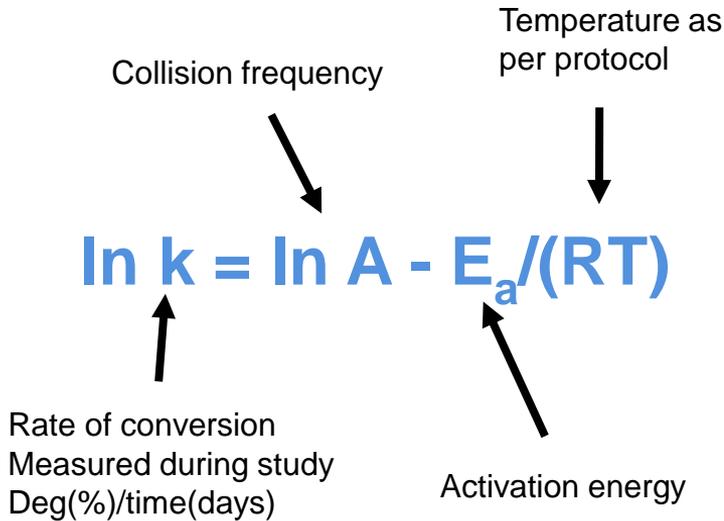
- Parenteral, topical and ophthalmic formulation in Novartis
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Introduction to ASAP principles:

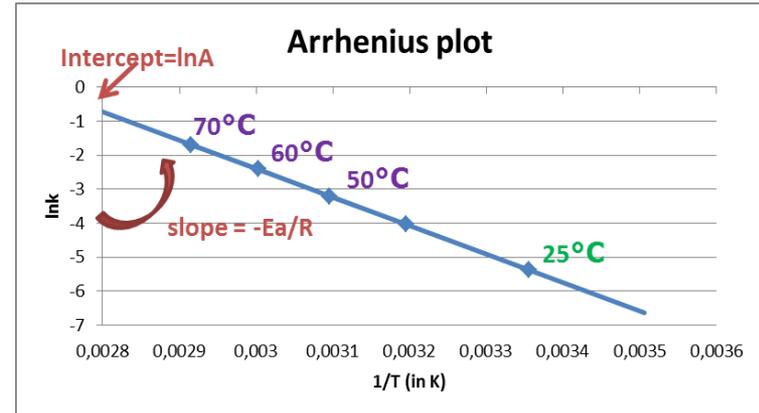
Accelerated Stability Assessment Program

	ICH	ASAP
Conditions	Long-term: 25°C/60%RH, 30°C/75%RH Accelerated conditions: 40°C/75%RH, 50°C	Broader range of conditions: 40°C to 80°C, 70 to 75%RH
Packaging	Primary container	Open dish / tight vial
Parameters tested	All parameters	Chemical degradation and Potency Other parameters under development
Length of study	Minimum 6 months	1 month
SL extrapolation	ICH allows 2 or 4 fold extrapolation (No kinetic consideration)	Kinetic understanding of the degradation and statistical based prediction
In development (variant selection/Technical stability)	<ul style="list-style-type: none"> ➤ Little or no degradation after 1M and/or 2M ➤ Uncertain relationship to long-term stability performance ➤ Extrapolation of 1M and/or 2M data to estimate shelf life is prone to error 	<ul style="list-style-type: none"> ➤ Isoconversion : no kinetic assumption ➤ Arrhenius equation (humidity corrected for solid) ➤ Statistical approach ➤ Confidence in shelf-life projections

Arrhenius Equation and protocol for liquid



Conditions	Time points
T (°C)	days
5	14
30	(7-14)
40	7-14
50	7-14
60	7-14
70	(7-14)



Humidity Corrected Arrhenius Equation and protocol for solids

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

Collision frequency

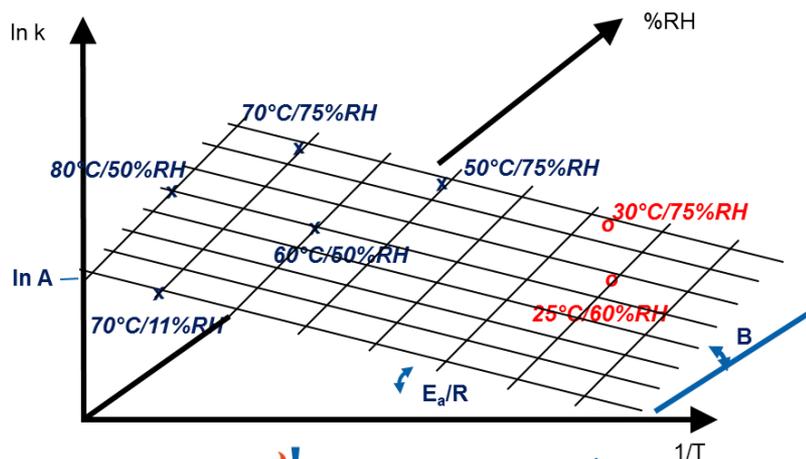
Rate of conversion

Activation energy

Humidity sensitivity factor

Relative humidity

Conditions		Time points
T (°C)	%RH	days
50	75	3-7-14
60	50	3-7-14
70	11	3-7-14
70	75	1-3-7-14
80	50	1-3-7-14



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#1- Project description and ASAP protocol

Background:

- Drug substance is poorly soluble in aqueous media
- Known formation of regio-isomer

Formulation strategy:

- Pure organic concentrate solution due to the poor solubility

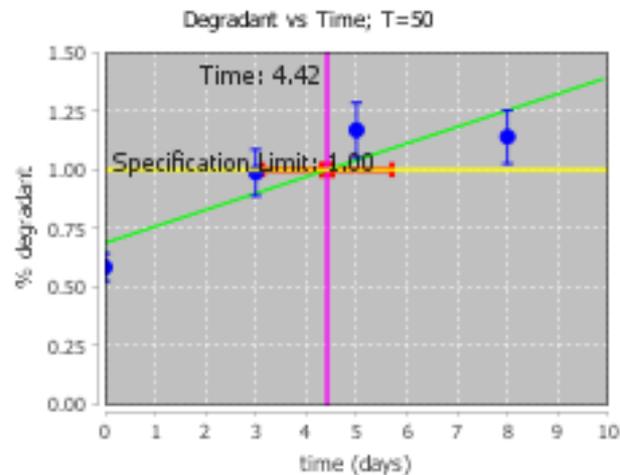
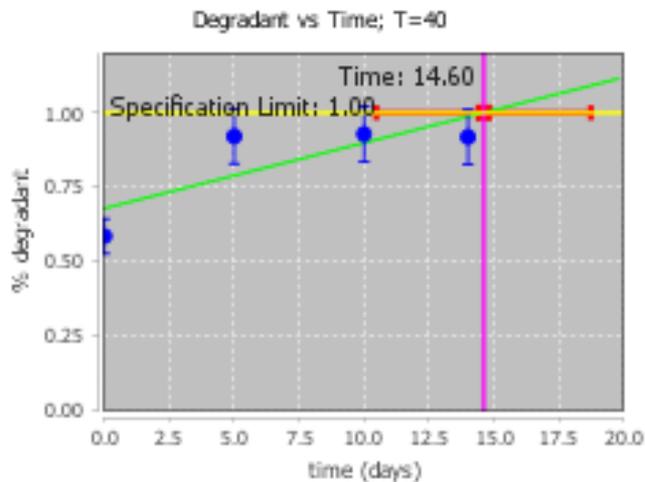
Formulations tested:

10 mg/mL of drug substance in 100% in

- Ethanol
- PEG300
- PG

	Storage conditions			
Test Plan	30°C	40°C	50°C	60°C
1 day				X
3 days			X	X
5 days		X	X	x
1 week	X	X	X	
2 weeks	X	X		
3 weeks	X			

#1 - Prediction for ethanol and PEG formulation



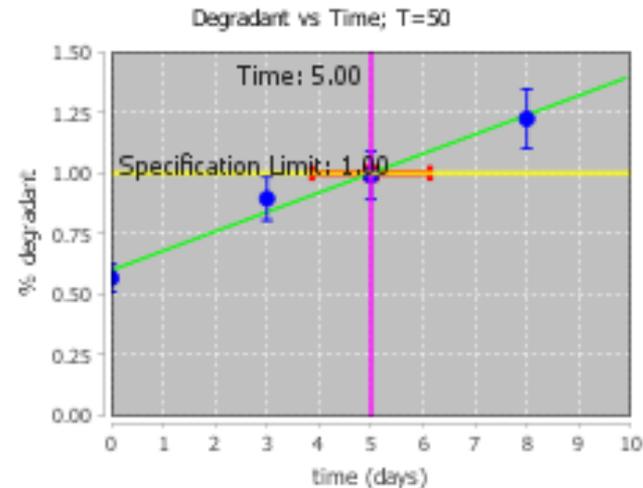
- Secondary degradation is observed, compromising accuracy of predictions (too optimistic compared to reality).
- Current prediction is still too short at 5°C:
 - ~ 6 months for ethanol formulation
 - Less than 3 months for PEG formulation.

#1 - Prediction for PG formulation

Arrhenius parameters

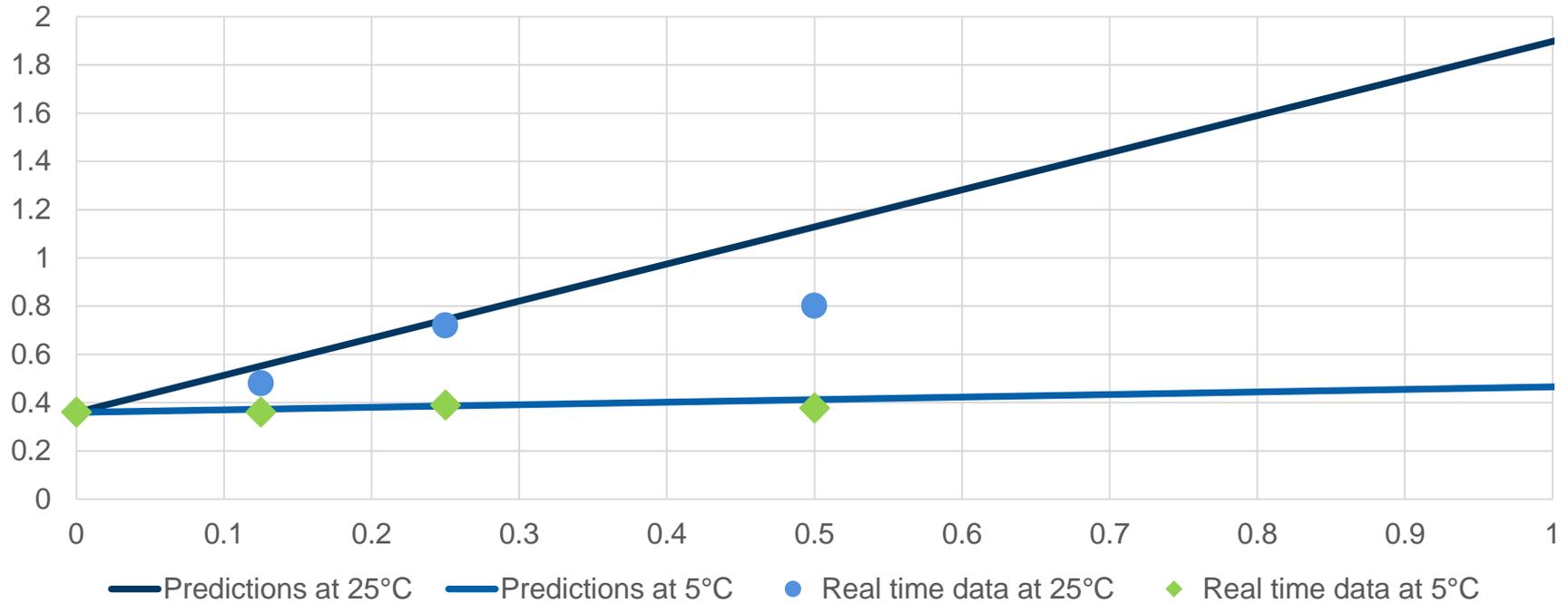
InA	31.8	
Ea	22.0	kcal/mol
R2	0.99	
Q2	0.95	

Parameters	Current formulation	SIMULATION Lower initial value	SIMULATION Higher spec
Specification	1.0%	1.0%	1.5%
Initial value	0.57	0.2	0.57
Mean SL at 5C	4 y	7.9 y	9 y
Confidence to pass 2 years at 5C	80%	99%	93%
Mean SL at 25C	0.3 y	0.5 y	0.6 y



- Linear kinetic for all conditions
- Good Arrhenius fit
- Predictions acceptable at 5°C
- Potential improvement:
 - Lowering initial value
 - Increasing specification

Comparison real time data vs ASAP prediction



Prediction was made linear to overcome degradation conversion. Real time data reflect expected degradation profile complexity

➤ No impact on the decision or the shelf life

#1 - Conclusions

ASAP enabled:

1. **successful selection of early phase clinical formulation in less than 6 weeks**
2. prediction of shelf life with a high confidence degree and good fit with long term data generated on selected formulation
3. team confidence for an early initiation of manufacturing activities
4. scientific understanding of the chemical degradation pathways and excipient compatibility

#2 – Formulation improvement —organic concentrate

1. Current formulation was physically unstable at 2-8°C thus storage condition was 25°C with limited shelf-life (18 months) due to the formation of Atropisomer which is temperature sensitive.
2. Oxidation was not a problem for the current formulation
3. Development of an alternative formulation was required
4. 2 PEG based formulations

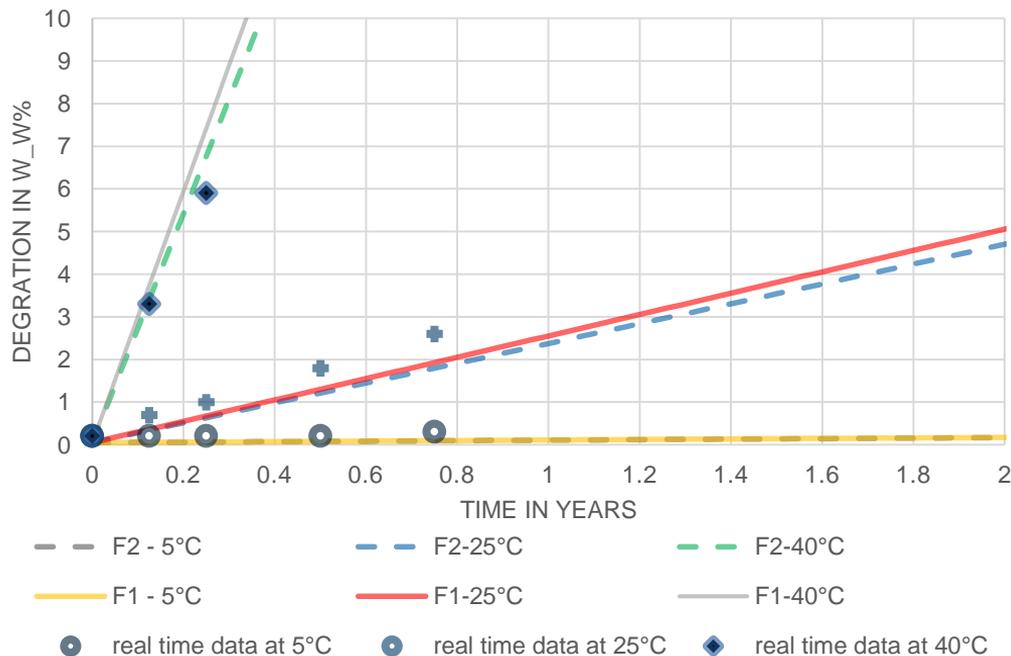
	Storage conditions				
Test Plan	5°C	25°C	40°C	50°C	60°C
1 week	X	X	X	X	X
2 weeks	X	X	X	X	X
3 weeks	X	X	X	X	X

#2- Prediction for atropisomer (spec. 4.9%)

	F1	F2
lnA	43.2	45.0
Ea (kcal/mol)	28.5	29.7
R ²	1	1
Predictions at 5°C	> 5y	> 5y
Probability to pass 3 years at 5°C	100%	100%
Predictions at 25°C	1.8 y	1.9 y
Probability to pass 18 months at 25°C	81 %	95%

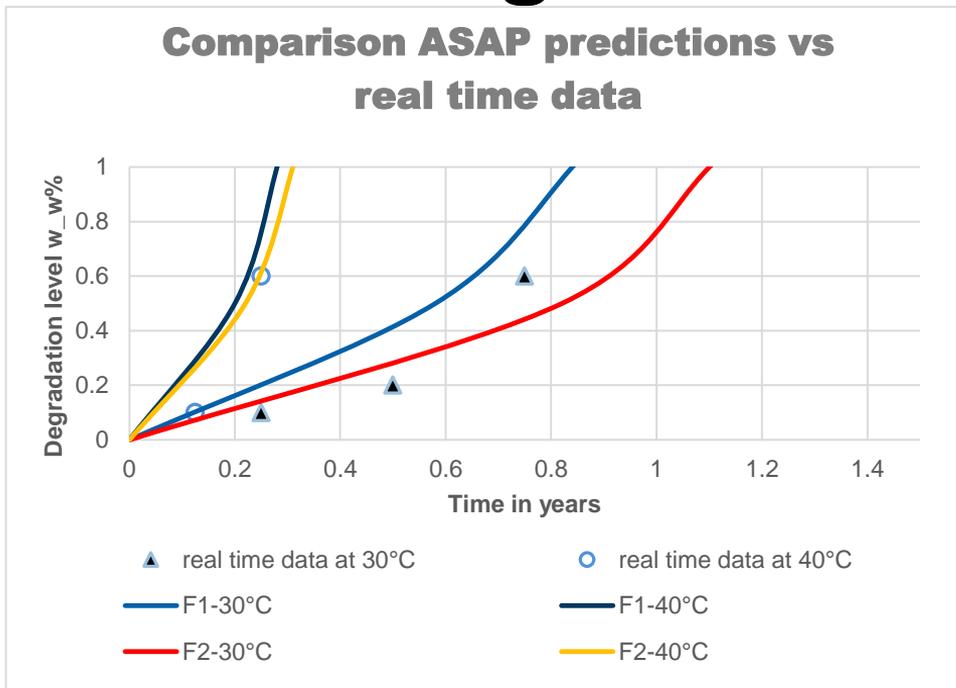
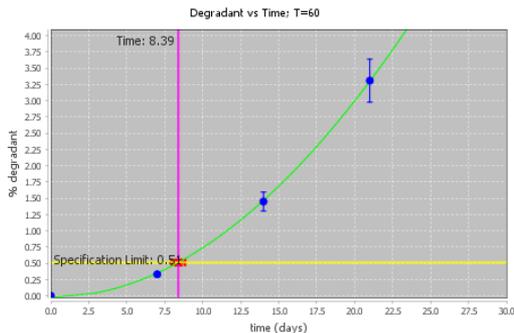
- Linear kinetic and good fit
- No significant difference between 2 formulations
- Formulation stable at 5°C
- Good fit with real time data of selected formulation

Comparison ASAP predictions vs real time data



#2 - Prediction for oxidation degradant (spec. 0.5%)

	F1	F2
InA	28.2	35.5
Ea	20.6	25.2
R2	0.93	0.95
Predictions at 5C	> 5y	> 5 y
Probability to pass 3 years	98 %	99%
Predictions at 25C	1 y	1.7 y
Probability to pass 18 months	20 %	72%



- Exponential kinetic
- F2 gave better SL and product would be stable at lower temperature

#2 - Conclusions

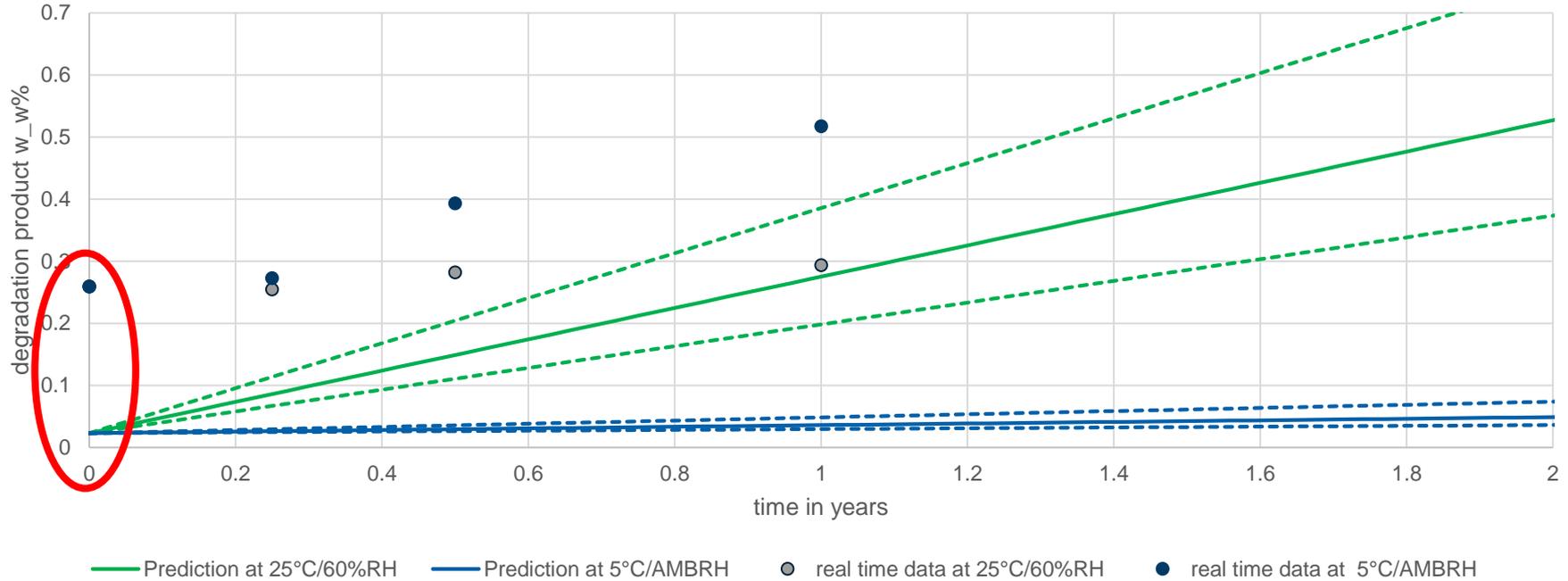
- Fast selection of new CSF variant
- Especially, due to the kinetic of the oxidation degradant, shelf-life prediction would have required at least 12 months real time stability
- **Gain in development time : 12 months**
- Good fit between real time and ASAP predictions
- The API is sensitive to oxidation thus, the impact of excipient quality (e.g formation of peroxides) to be further evaluated

#3 What if Clinical batch is worst than the ASAP batch

1. Screening of 12 formulations (6 liquid in vial and 6 lyophilisates)
 2. Predictions for liquid in vials >3 y at 5°C and around 0.5y at 25°C
 3. Predictions for lyophilisate ≥ 2 years at 25°C
- Team selected one of the lyophilisate formulation

 - Comparison real time vs prediction

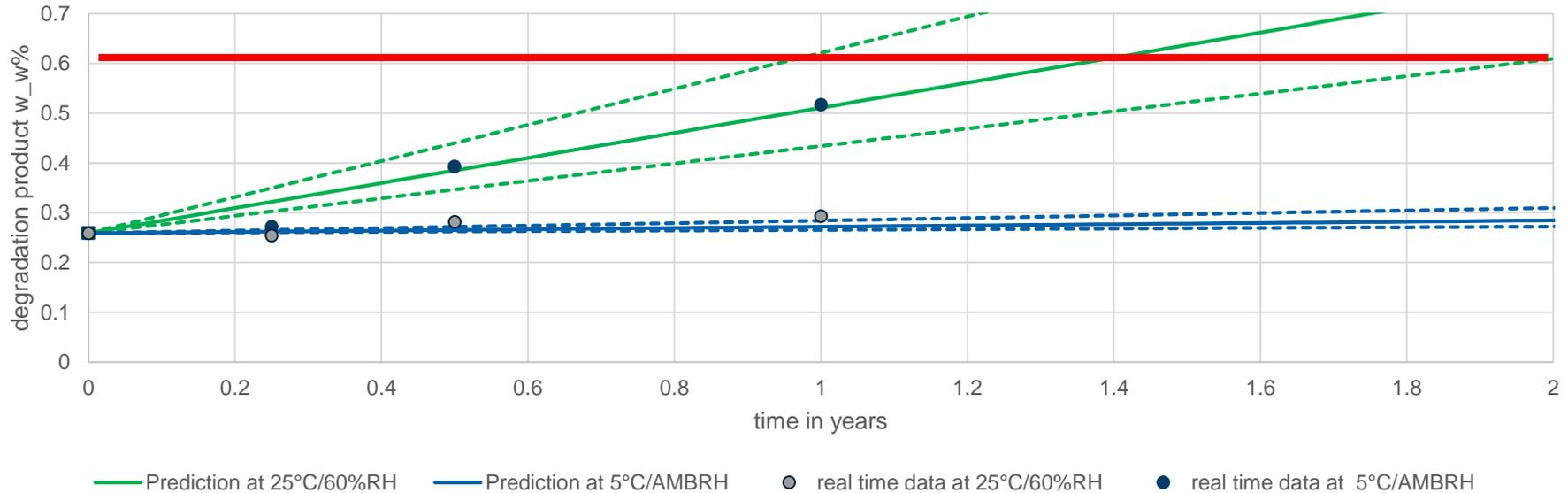
Comparison predictions vs real time data



Comparison is very difficult as such since drug substance batch used was not the same with very different initial value of the impurity

➤ Prediction modify to fit new initial value

Comparison predictions vs real time data after changing T0 for ASAP



- Degradation kinetic was not modified as it can be expected for linear trend
- Shelf life prediction much shorter at accelerated condition but still sufficient at long term condition

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Background on project

1. Drug substance:

- Very unstable drug substance: frozen long term storage condition
- Shelf life limiting degradant is above specification limit at 1 month 25°C/60%RH
- Amorphous drug substance, very hygroscopic (~15% water at ambient RH)
- Forced degradation: hydrolysis and rearrangement

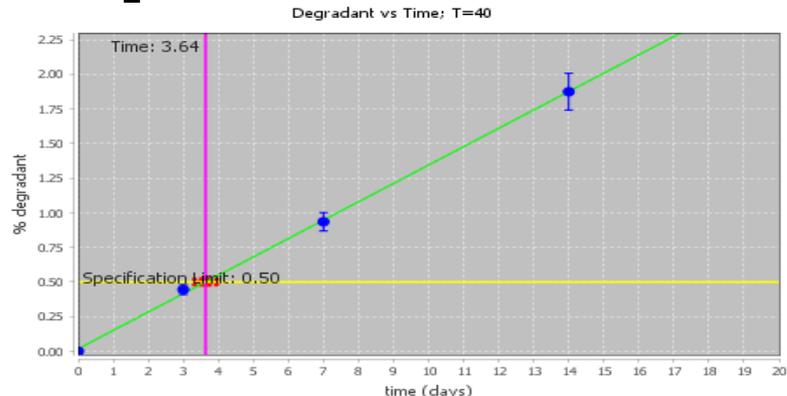
2. Drug product:

- Quite unstable liquid solution, selected without ASAP
 - Liquid in vial at pH 7 with phosphate buffer
 - Current storage condition: store below -15°C
- ASAP#1 was run on clinical batch to confirm instability and understand better the behavior and degradation profile

ASAP#1 – Phase 1 Liquid Formulation

Temperature	Time point (days)
25°C	30
30°C	14, 30
40°C	3, 7, 14
50°C	1,3, 7

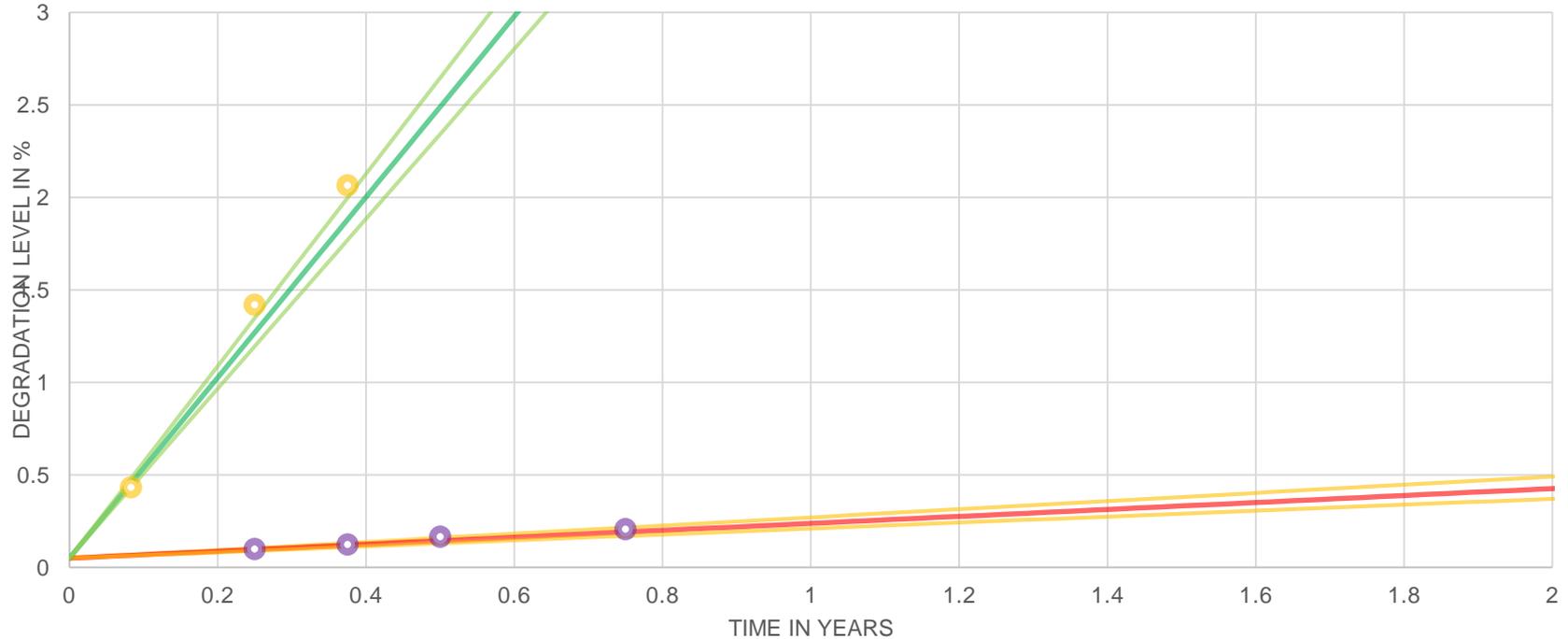
InA	41
Ea	27
R2	0.99
Q2	0.99
Prediction at 5C	2.4 y
Probability to pass 2y at 5C	88%
Prediction at 25C	< 2 months
Probability to pass 6M	<1%



Kinetic at 40°C

- ✓ Linear kinetic (40°C graph)
- ✓ Good model/fit
- ✓ 1 main degradant
- X Do not reach 3 years shelf life at 5°C
- X Do not reach 2 months at 25°C
- X Frozen storage for liquid formulation

Comparison real time data vs ASAP prediction at 5°C and 25°C



— Prediction at 5°C ● real time data at 5°C
— Prediction at 25°C ● real time data at 25°C

Assessment and next step

1. ASAP predictions vs real time data – excellent match!
2. ASAP Outcome: Very unstable formulation confirmed
3. Degradation pathway learning from ASAP#1:
 - 1 main degradant and 2 minors
 - All degradation products observed are due to hydrolysis
 - No oxidation observed

- pH influence? Not option since solubility decrease with pH
- Change to lyophilisate
- ASAP#2: screen 3 LYO formulations with different bulking agents

	Storage conditions			
Test Plan	Initial	30°C	40°C	50°C
3 days				1
1 week			1	1
3 weeks	1	1	1	1

ASAP#2 Stability data for 3 lyophilisate formulations

ASAP prediction

Name	Name	Assay(%)	Main deg	SUM
Mannitol	initial	97.54	<loq	0.09
	3w/30C	99.28	0.10	0.19
	3w/40C	98.50	0.19	0.29
	3w/50C	98.07	0.35	0.59
Saccharose	initial	95.43	<0.05	<0.05
	3w/30C	95.26	<0.05	<0.05
	3w/40C	95.44	<0.05	<0.05
	3w/50C	103.30	0.27	0.37
Mannitol/ Saccharose	initial	96.31	<0.05	<0.05
	3w/30C	96.95	<0.05	<0.05
	3w/40C	97.57	<0.05	<0.05
	3w/50C	96.89	<0.05	<0.05

ASAP#3 Mannitol formulation: Prediction for deg 1 (spec limit 0.5%)

Parameters	RRT0.75
InA	24.3
Ea	18.3
R2	0.99
Q2	0.88
Prediction at 5C	> 5 y
Probability to pass 2y at 5C	89%
Prediction at 25C	0.9 y
Probability to pass 6M	85%

- Similar degradation profile as the liquid formulation – 3 hydrolysis degradants
- Formulation stable at refrigerated conditions or even room temperature for the saccharose/mannitol formulation
- Continue formulation optimization with DoE/ASAP
- Combine chemical and physical parameters

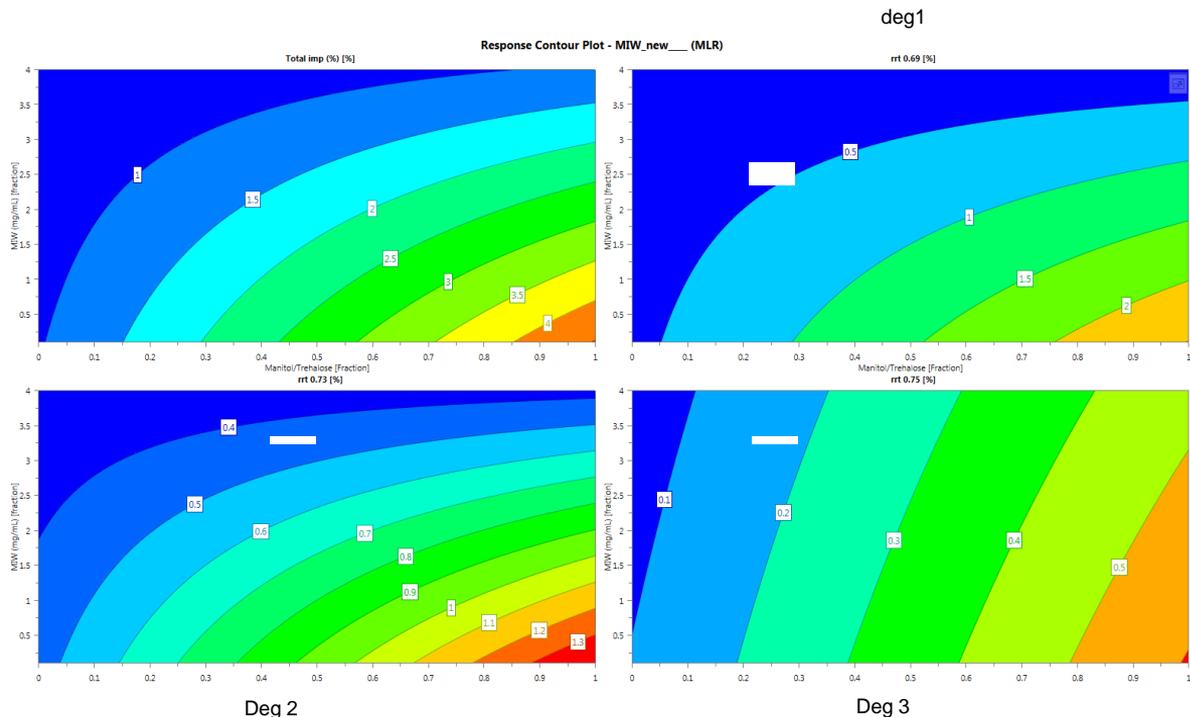
DoE set up

1. Screening parameters:
 - Bulking agent choice and concentration (Mannitol/trehalose ratio and amount – isotonic reconstituted solution)
 - Buffer concentration (phosphate buffer from 5 to 15 mM)
 - DS concentration (0.1 mg/ml to 4 mg/ml upon reconstitution)
2. Excluded parameters:
 - To minimize composition change form Phase 1 Clinical Trial to Phase 2 (BA/BE)
 - No pH change, no buffer change (no other buffer in marketed DP for the target)
 - Saccharose excluded and replaced by Trehalose since saccharose was never used in this type of application.
 - Lyophilisation cycle process: Same conservative process parameters was applied to all formulations.
3. Responses:
 - DoE responses:
 - Shelf life **R2 is too low – no proper interpretation**
 - Shelf life limiting impurities at 60°C
 - Full degradation of the drug product at 60°C
 - Visual appearance of the cake
 - Reconstitution time **All sample below 1 min no effect of all parameters tested**

Impurity results after 34 days storage at 60°C: (Contour plots DS vs Mannitol/Trehalose ratio)

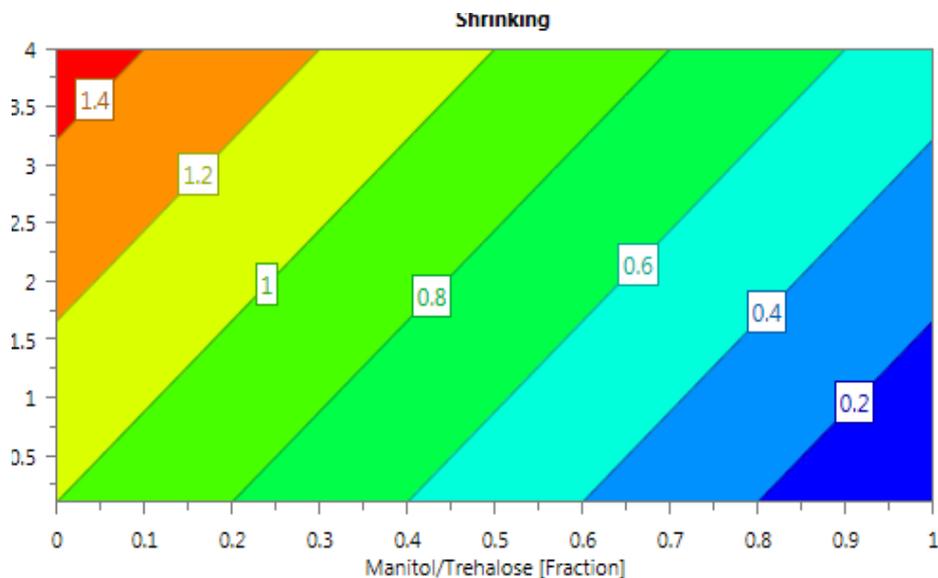
Summary on Contour plots

1. Higher Trehalose and higher API concentrations results in lower values for all impurities as expected based on that main effect plot.
2. The most stable formulation would have the highest amount of Trehalose and highest amount API.
3. The impact of both parameters is mainly seen for 2 degradants and the total deg.
4. Non linear effect of Trehalose/Mannitol ratio



Visual appearance of the cake

- Higher amount of Trehalose results in more shrinking of the cake. (2= high shrinking, 1= low shrinking, 0= no shrinking)
- Buffer and API concentration have no impact on shrinking of the lyo-cake.



Mannitol/Trehalose	Buffer (mM)	API (mg/mL)	Shrinking
0	5	0.1	1
1	5	0.1	0
0	15	0.1	1
1	15	0.1	0
0	5	4	2
1	5	4	0
0	15	4	1
1	15	4	1
0.5	10	2.05	1
0.5	10	2.05	1
0.5	10	2.05	1

Conclusions of DoE

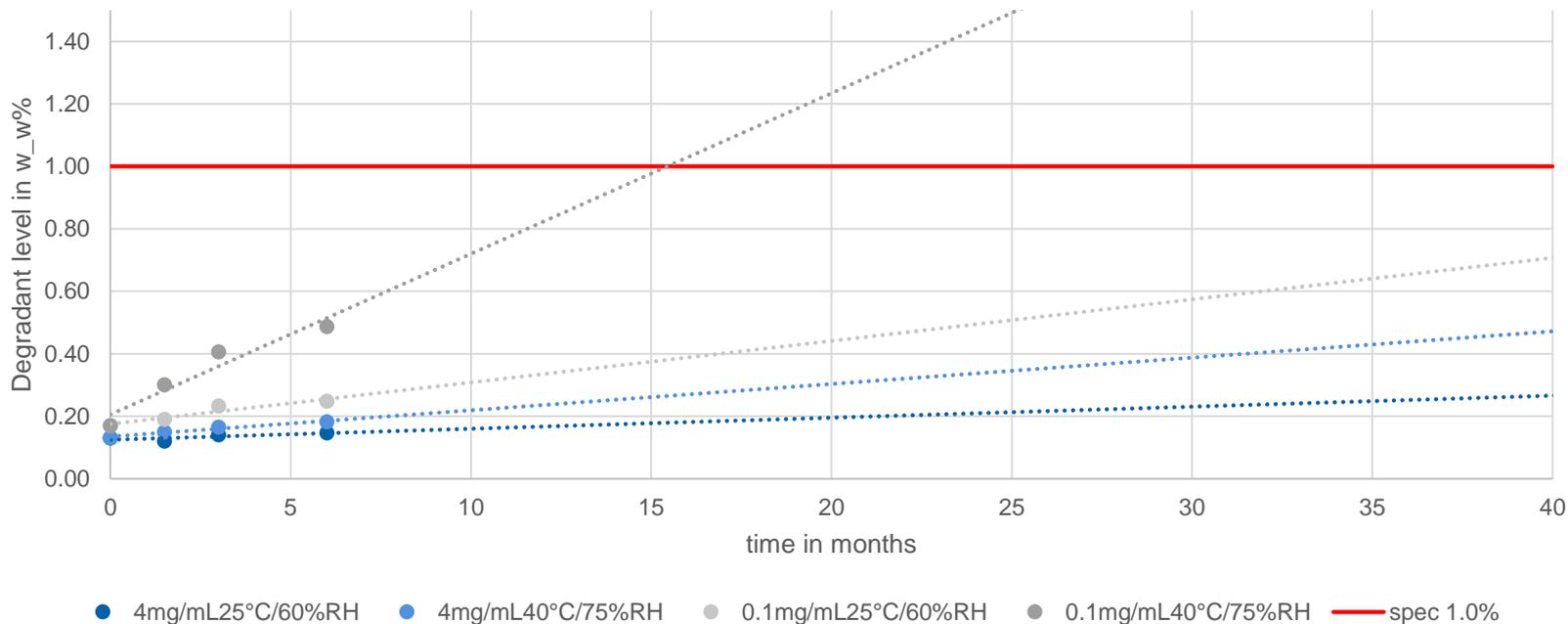
1. Drug product:

- Chemically stable formulation in the whole range of API concentration using 100% Trehalose but cake appearance better with Mannitol
- Cake appearance was optimized to be able to use 100% Trehalose
- **Lyophilisate formulation with a shelf life predictions of more than 3 years at 25C/60%RH**

2. DoE with ASAP

- ASAP predictions are still difficult to include in DoE – error is too high
- Individual impurities or total deg are still better but missing the kinetic aspect
- Improve set up to be able to use ASAP predictions or individual Arrhenius parameters in the DoE model

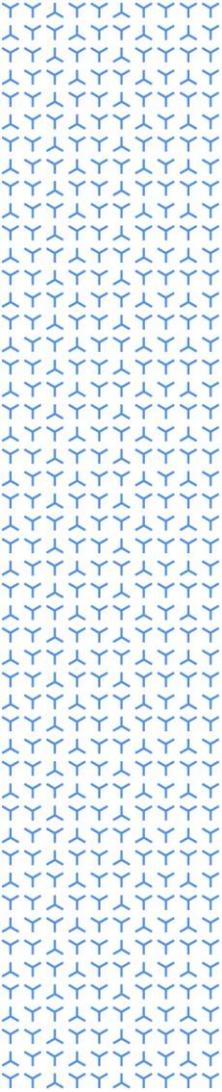
Main degradant trend in ICH stability



As observed in the DoE degradation rate is faster with the low strength but still acceptable. Real time data confirmed the 3 years shelf life at room temperature.

Implementation within development

1. ASAP is now the preferred tool within formulation development across all portfolio, when applicable
2. Its use accelerate the development especially in early phase
3. Develop real kinetic understanding of the degradation profile
4. Faster generation of stability data to support decisions
5. **QUICK AND GOOD!**



Eric Aubin
Stephane Auvray
Guy Bruat
Carol Goalard
Davina Sohier
Marc Schoenhentz
Fabienne Wildi

Thank you