ASAP for parenteral formulation development – solutions and lyophilisates

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Agenda

- Parenteral, topical and ophthalmic formulation in Novartis

- Formulation development –

from unstable liquid formulation to stable lyophilisate using ASAP and/or DoE

- ASAP study on lyophilisate –

Which approach to use - open dish or closed vial?

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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

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Types of parenteral formulation developed at Novartis using ASAP

- **Liquid in vials**
- **Lyophilisate in vials**
- Liposomes and Mixed micelles
- Gel and Cream

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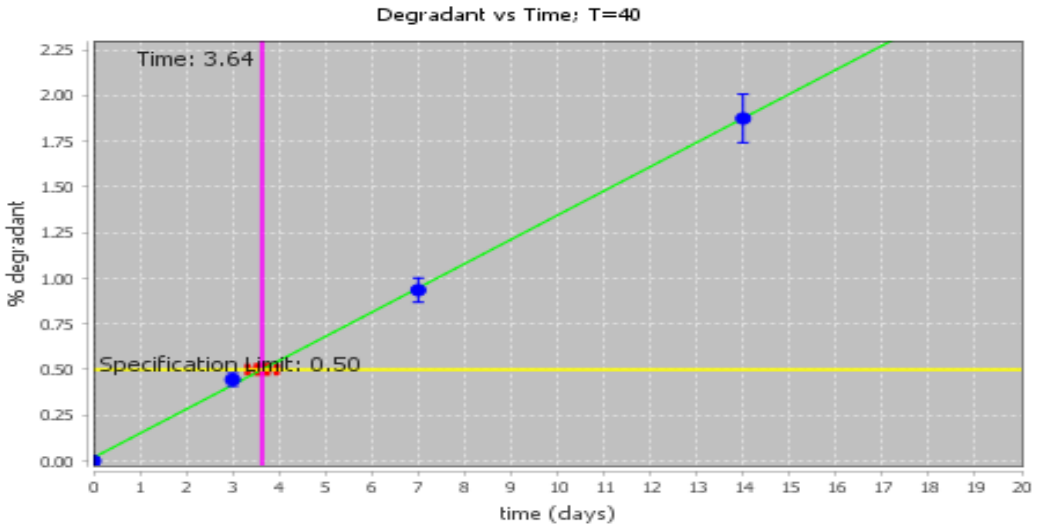
Background on project

- 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: potential oxidation and hydrolysis
- 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

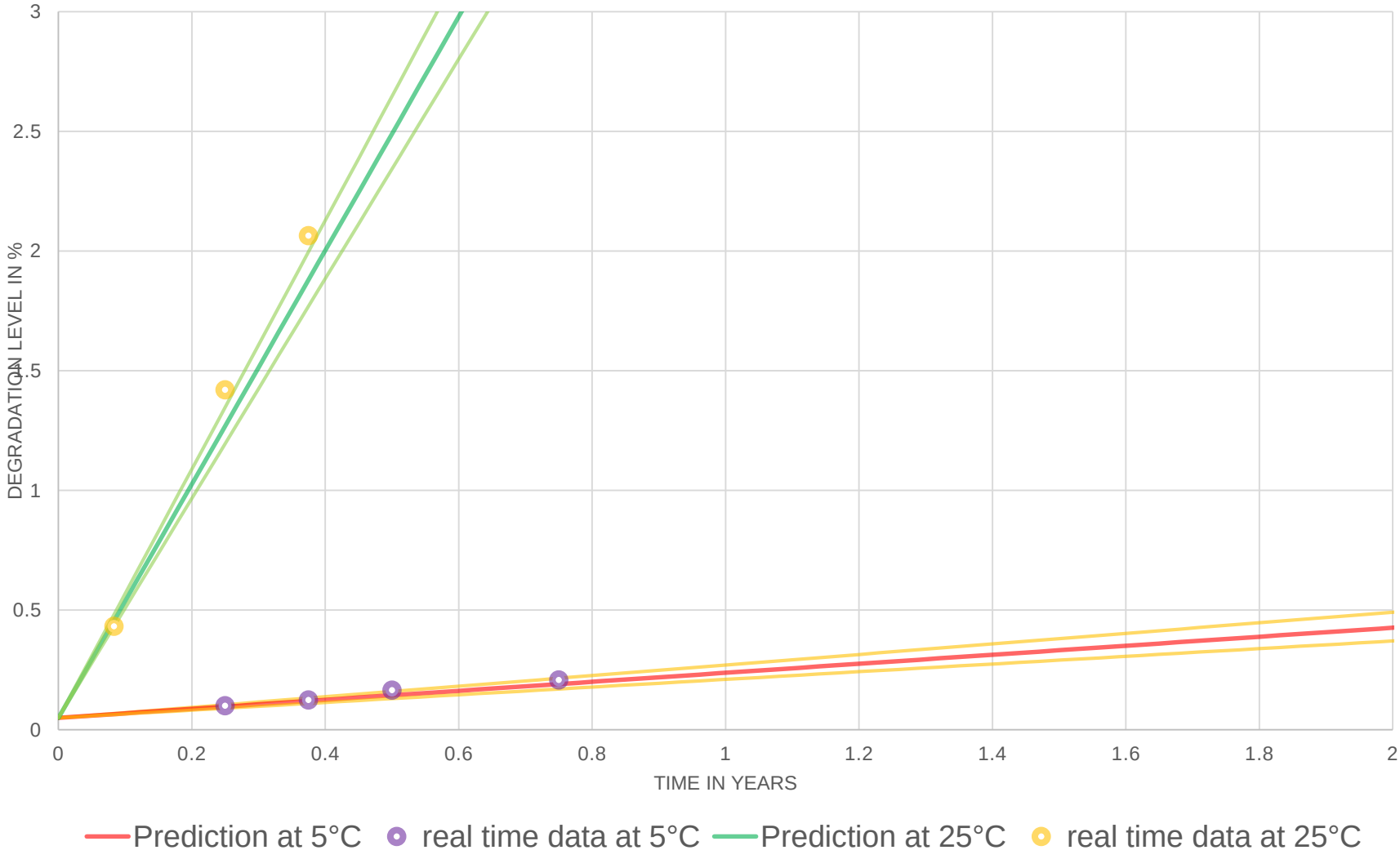


Kinetic at 40°C

lnA	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%

✓ 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



Assessment and next step

- ASAP predictions vs real time data – excellent match!
- ASAP Outcome: Very unstable formulation confirmed
- 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?

➢ ASAP#2
- Screen pH from 5 to 7
- Use very lean ASAP protocol based on existing knowledge

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

ASAP#2 Prediction for Main degradant (spec limit 0.5%) in a pH screening

pH	5.0	5.5	6.0	6.5	7.0
lnA	NA	44.9	29.6	32.4	35.5
Ea	NA	31.2	20.8	22.2	23.5
R2	NA	0.89	1	1	1
Q2	NA	0.7	0.99	1	0.99
Prediction at 5C	> 5 y	> 5 y	4.2 y	3.5 y	1.7 y
Probability to pass 2y at 5C	100%	100%	85%	89 %	28%
Prediction at 25C	> 5 y	3 y	0.3 y	[illegible] y	0.1 y
Probability to pass 6M	100%	99%	13 %	< 1%	< 1%

Conclusion on ASAP #2

- Clear pH effect – DS is more stable at lower pH
- Drug substance solubility decreases at low pH
- pH effect on clinical effect is not known and phase I already running

➢ Liquid formulation with lower pH is not an option

➢ Change to lyophilisate

➢ ASAP #3: 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

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ASAP#3 Stability data for 3 lyophilisate formulations

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 prediction

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

Parameters	RRT0.75
lnA	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

- Screening parameters:
  - Bulking agent choice and concentration (Mannitol/trehalose)
  - Buffer concentration (phosphate buffer from 1 to 5 mM)
  - DS concentration (4 to 0.1 mg/ml upon reconstitution)
- Excluded parameters:
  - Change of buffer – no other buffer known for the target
  - No other component in the formulation
  - Lyophilisation cycle process
- Responses:
  - Chemical degradation/Shelf life predictions
  - Cake appearance
  - Reconstitution time

DoE

Variable / Parameters	Low (-1)	Center point (0)	High (+1)
API (mg/mL)	0.1	2.0	4.0
Buffer NaH_2PO_4 (mM)	5	10	15
Mannitol : Trehalose dihydrate ratio (mg/ml)	0 : 60	15 : 30	30 : 0

- Storage conditions: -20°C, 30°C, 40°C, 50°C, and 60°C
- Storage time: 34 days.

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

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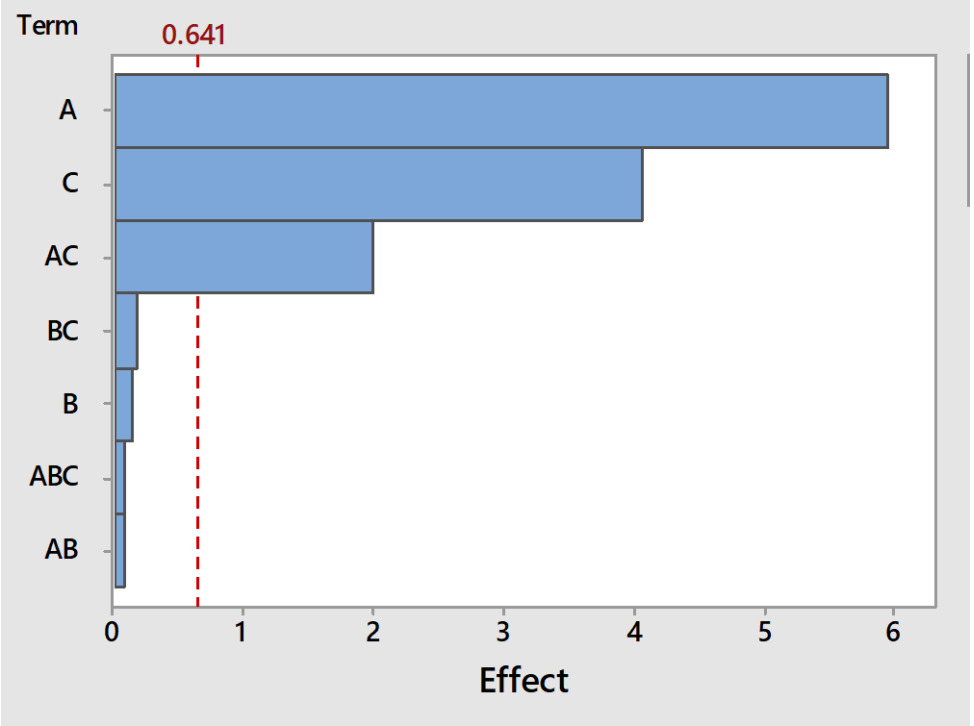
Impurity results after 34 days storage at 60°C (Pareto Charts)

The most significant parameters on individual impurities and total degradation are listed below:

- **Mannitol / Trehalose ratio (A).**
- **DS concentration (C).**
- **Interaction effect of (Mannitol/Trehalose * DS = AC).**

The concentration of buffer (B) is not signification.



A = Mannitol/Trehalose
B = buffer concentration
C = API concentration

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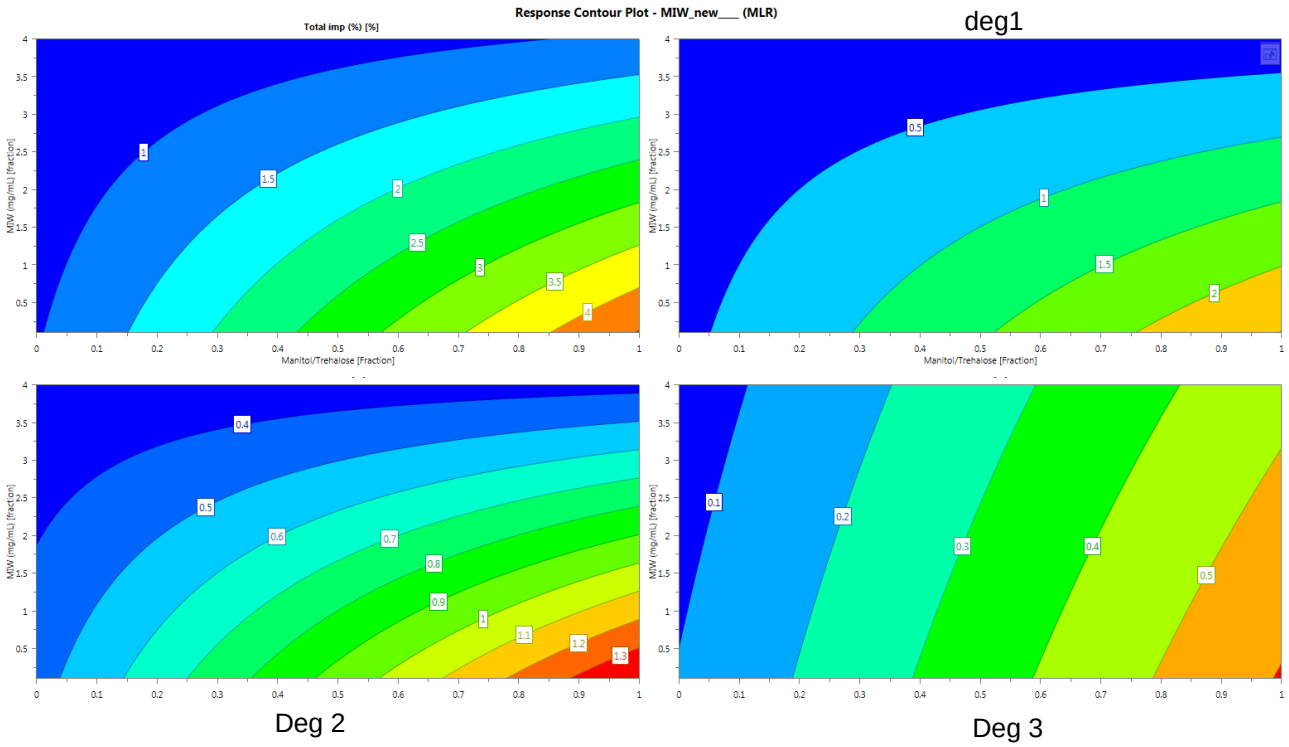
Impurity results after 34 days storage at 60°C: (Contour plots DS vs Mannitol/Trehalose ratio)

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



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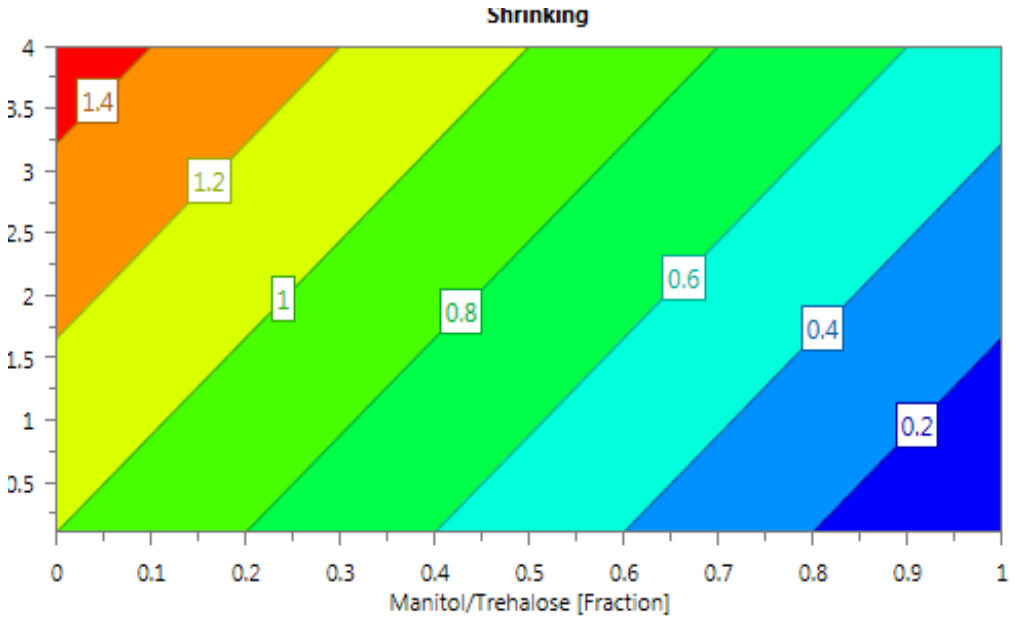
Visual appearance of the cake

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



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

- 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**
- 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

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Goal

2 ASAP set ups are possible for Lyophilisate in parenteral use :

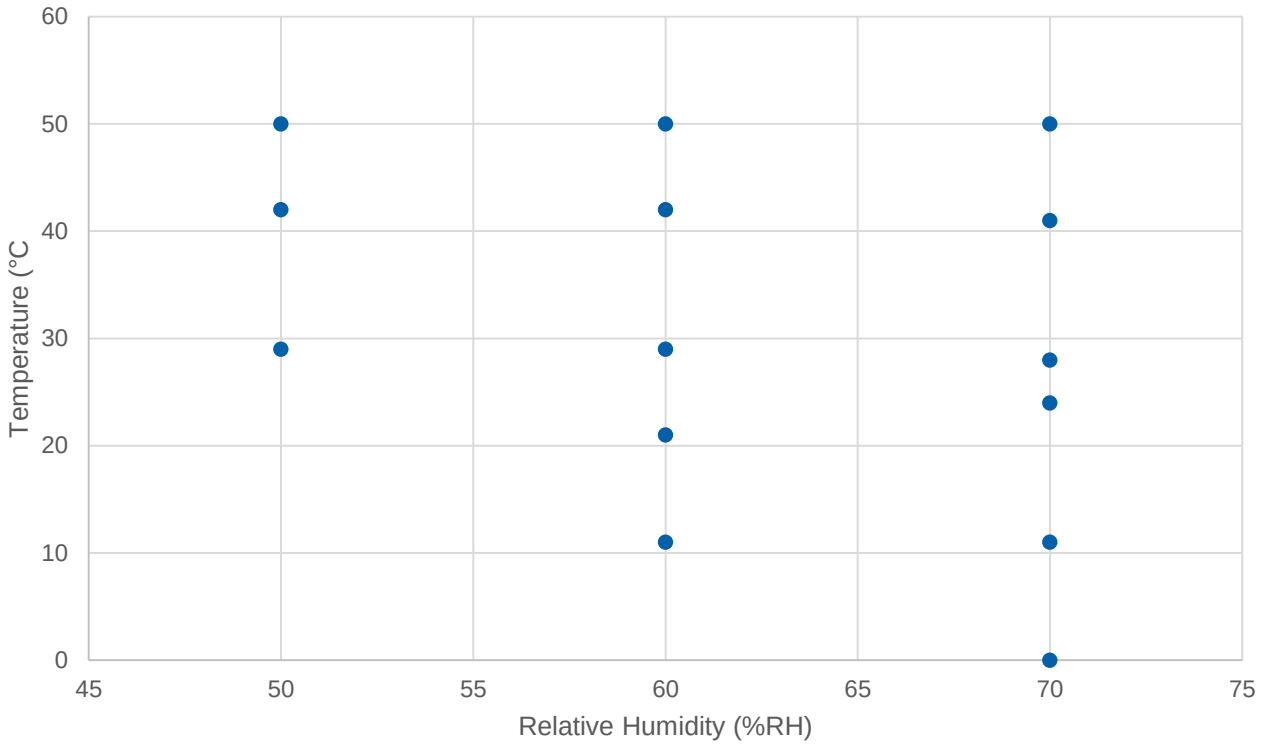
- Directly in the closed vial
  - Final product is in very tight container so humidity intake negligible over stability
  - Protocol is very limited since only temperature is screened -Much less product consumed
- Open dish as for classic powder evaluation
  - Influence of initial water only doable with open dish
  - Might not be required if LYO cycle is optimized

Compare prediction accuracy of closed vial vs open dish on a selected lyophilisate formulation for parenteral use.

Selection of formulation

- Comparison of the 2 ASAP approaches was done on the Mannitol formulation at low API concentration tested prior in the optimization of lyophilisate formulation (DoE)
  - Sufficient degradation was observed
  - One major degradant,
  - Linear kinetic
  - ASAP model is predictive for this molecule
- 3 studies in parallel:
  - ASAP in closed vials
  - ASAP open dish
  - Some long term vials for comparison

ASAP protocol for open dish study



- Time points: 4 or 7, 14 and 28 days
- More conditions and time points than usual to anticipate potential over degradation or not enough degradation

ASAP protocol for closed vial and long term

ASAP protocol

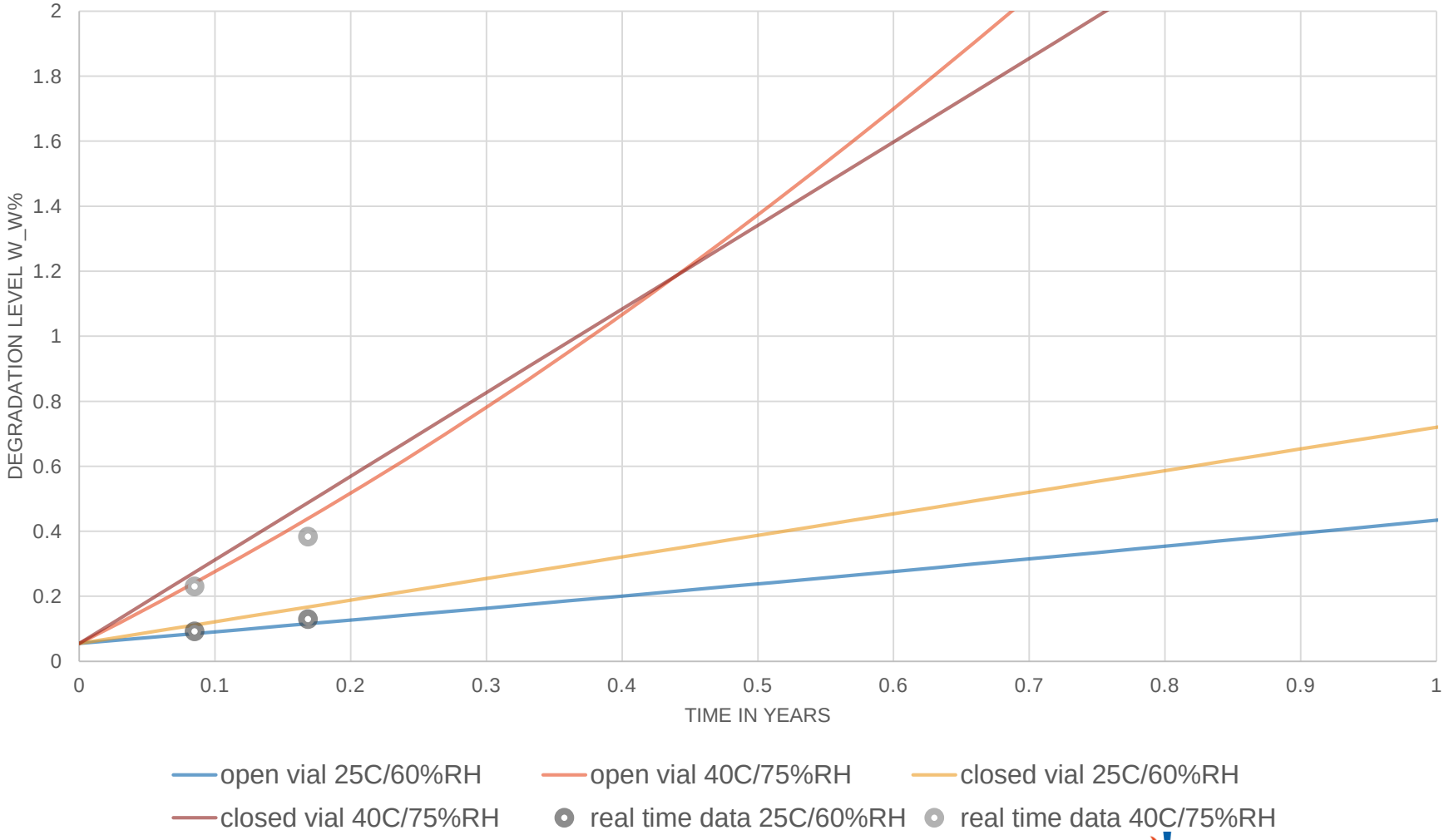
Temperature (° C)	Time (days)		
	14	20	28
initial	-	-	x
50	x	x	x
60	x	x	xx
70	x	xx	x

Long term storage

Conditions	Time (months)			
	1	3	6	BU
25C/60%RH	xx	xx	xx	xxx
40C/75%RH	xx	xx	xx	xxx

X = 1 vial

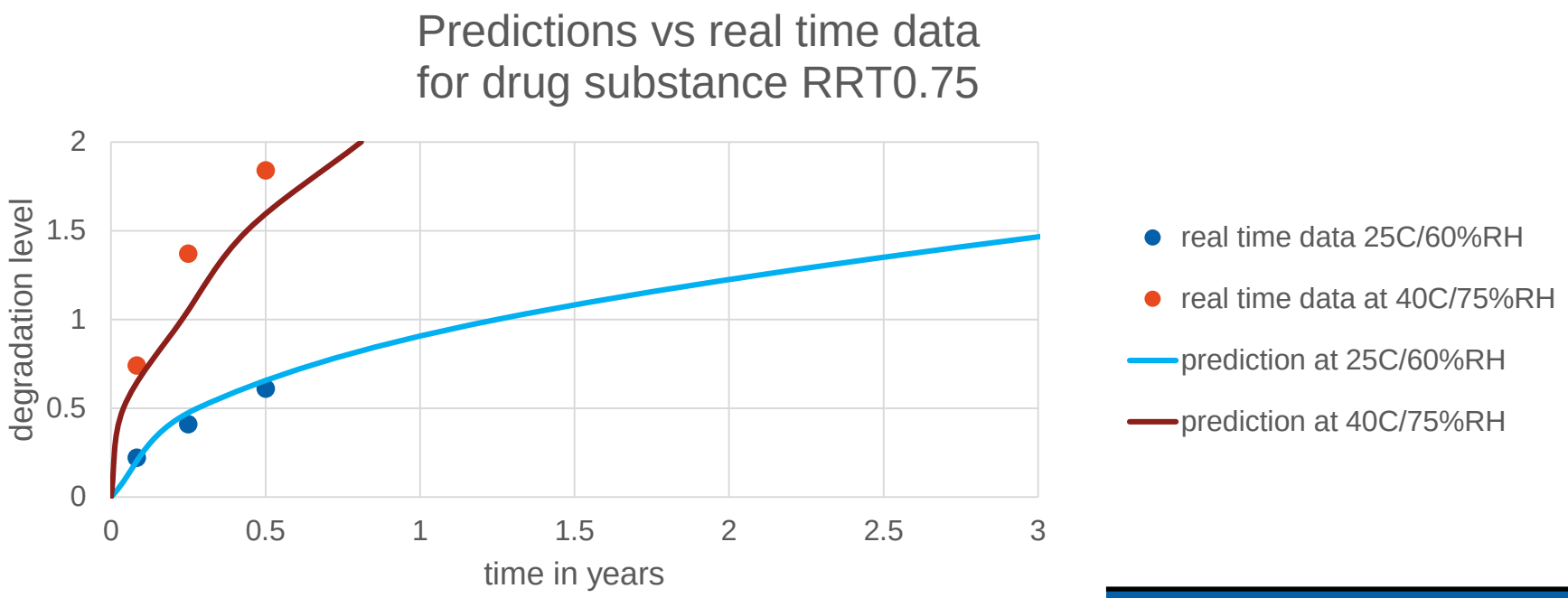
Comparison predictions vs real time data for Main deg



Outcome

1. Real time data are fitting better with the open dish predictions but no high differences
2. Closed vial predictions are the worst case
   - Lower lnA and Ea
   - Small green house effect?
3. For lyophilisate tested, B value seems low
   - Hydrolysis product
   - Very high water intake
   - Degradant is much higher in liquid so a high B value could be expected
   - Compare with drug substance which is an amorphous API
   - ➢ Same open dish protocol for drug substance to evaluate impact of bulking agent on stability

Drug substance ASAP predictions



- Degradation kinetic for RRT0.75 in DS is diffusion
- Similar Arrhenius parameters to the lyophilisate open dish
- More degradation than in lyophilisate due to a much higher initial water content (~15%)
- <u>No influence of lyophilisate excipients on stability: initial water is the main difference between lyophilisate and drug substance stability!</u>

Arrhenius Data	Lyo	DS
lnA	31	28
Ea	23	21
B	0.02	0.02
R2	0.96	0.94
Q2	0.93	0.86

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Conclusions ASAP approaches

1. Quick and efficient development combing ASAP and DoE to improve formulation
   - Improve ASAP set up to include predictions as output for DoE studies

2. Closed vial predictions are close to real time and is much less resources and material consuming but give shorter shelf life than reality
   - Perform more open dish vs closed vials comparisons
   - Collect information on B values for more lyophilisate formulations on other formulation type and drug substance

Fabienne Wildi, analytical expert
Stephane Auvray, associate scientist
Carol Goalard, drug product project leader
Murad Rumman, formulation project leader

Thank you

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