ASAP implementation and use

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OF Johnson&Johnson

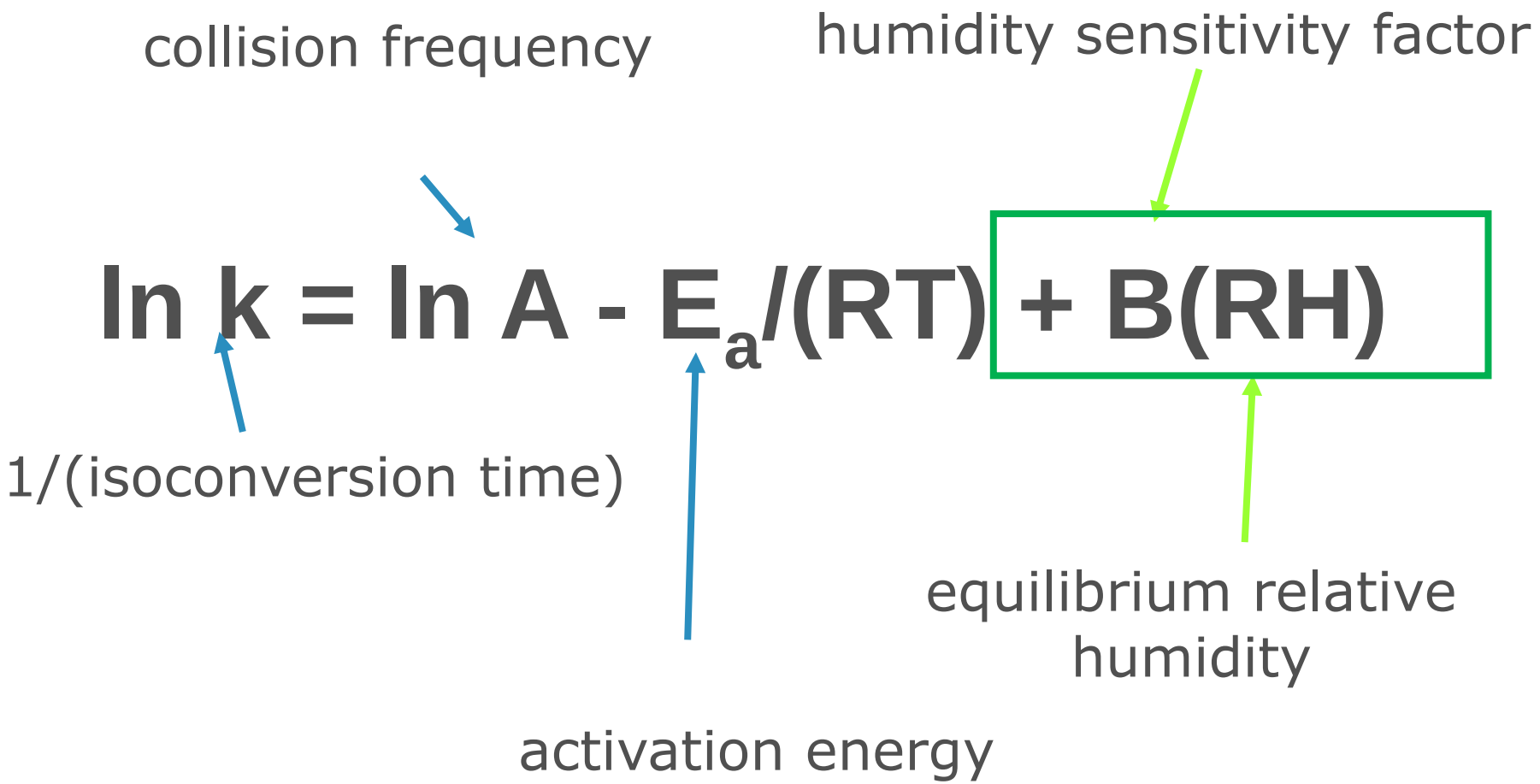
Introduction to ASAP principles

- Accelerated Stability Assessment Program
- Accelerated stress study (~ 1 month) :
  - *Solid dosage form*: evaluating impact of temperature and humidity on API stability on chemical degradation
  - *Liquid dosage form*: evaluating impact of temperature on API stability on chemical degradation
- Based on Arrhenius equation
- Statistical prediction of shelf life

ICH vs. ASAP methodology in Small Molecules

ICH	ASAP
Long-term: 25°C/60%RH, 30°C/75%RH **Accelerated conditions:** 40°C/75%RH, 50°C Immediate container Minimum 6 months	**Broader range of conditions:** (40°C to 80°C, 10 to 75%RH) Open dish studies 1month
In development time frame •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	•**Isoconversion** : no kinetic assumption •**Arrhenius equation (humidity corrected for solid)** •**Statistical approach** •Confidence in shelf-life projections
ICH allows 2 or 4 fold extrapolation (No kinetic consideration)	**Kinetic understanding of the degradation**

Humidity Corrected Arrhenius Equation



ASAP Protocol

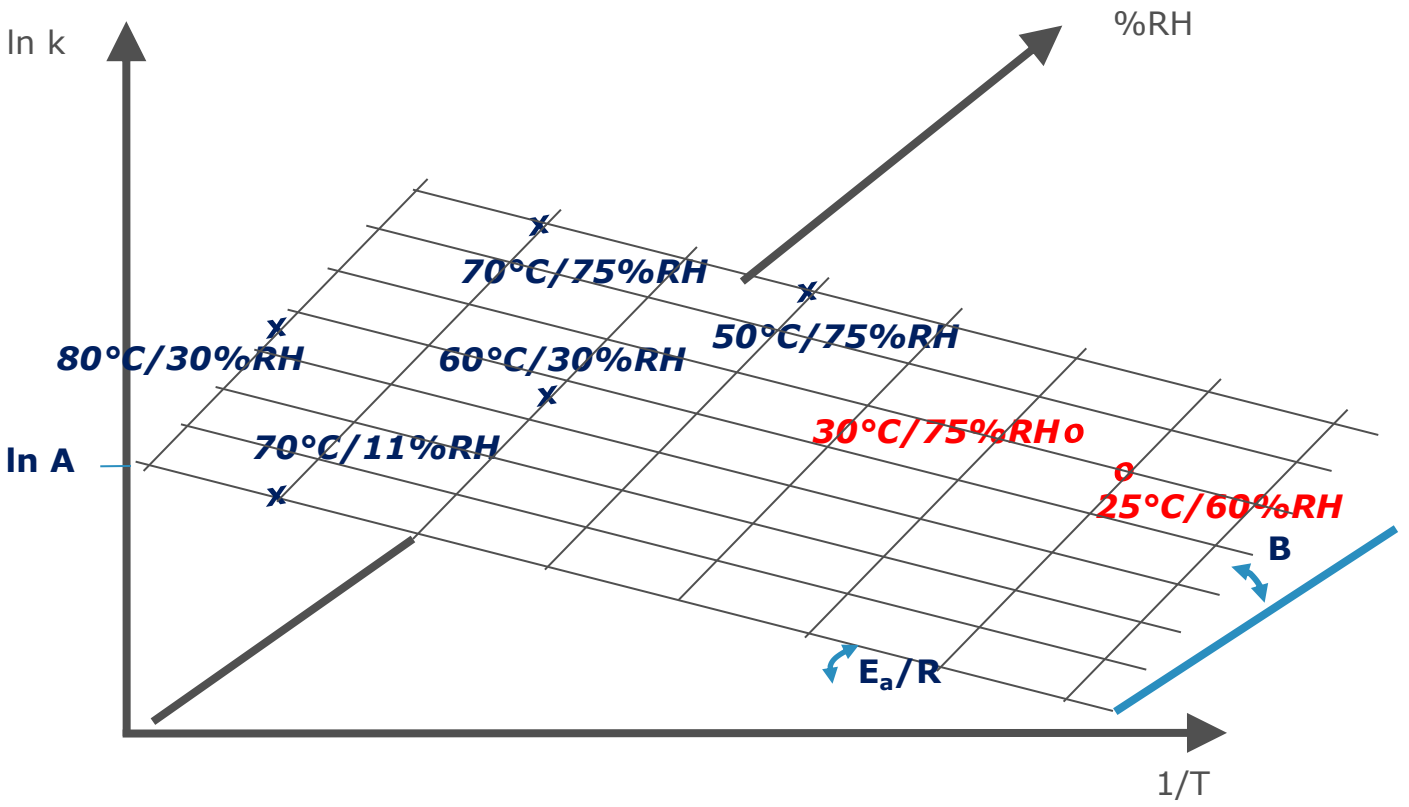
- General condition if no more information available
- Protocol can be applied to DS and DP

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

- Protocol needs to be adapted based upon stability of the DS or DP

ASAP Design of Experiment: Determining the Plane

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

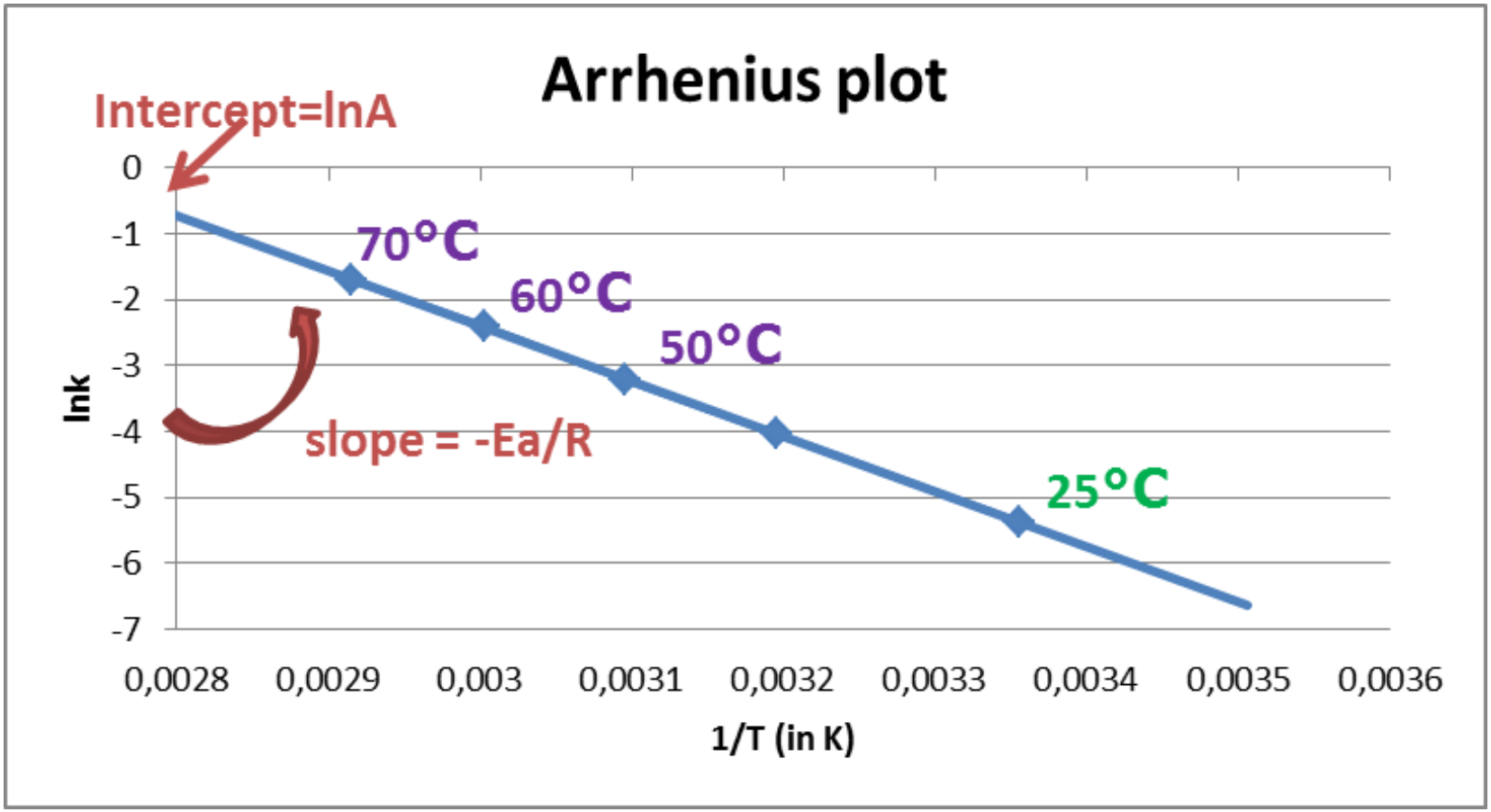


ASAP protocol for liquid formulation

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

- Protocol needs to be **adapted** based upon available stability information

ASAP Design of Experiment : determining the line for liquid



Potential Applications of ASAP

- NME selection screening
- **Shelf-life projections for Drug Substance and all Drug Product and filing support**
- Support filing of DS and intermediates
- **Fast formulation stability evaluation**
- **Packaging prediction to minimize screening study**
- Evaluation of process robustness

Case Study :
Shelf life prediction
Packaging recommendations

Initial ICH set up

Study ID	Packaging Information	Packaging Site
1	Alu/Alu blister	1 mg
2	Alu/Alu blister	5 mg
3	Alu/Alu blister	10 mg
4	PVC-Aclar/Alu blister	1 mg
5	PVC-Aclar/Alu blister	5 mg
6	PVC-Aclar/Alu blister	10 mg
7	PVC-PEPVDC/Alu blister	1 mg
8	PVC-PEPVDC/Alu blister	5 mg
9	PVC-PEPVDC/Alu blister	10 mg
10	HDPE bottle/PP Closure CR	1 mg
11	HDPE bottle/PP Closure CR	5 mg
12	HDPE bottle/PP Closure CR	10 mg

3 strengths, 4 packaging => 12 studies

Results for 5 mg

Condition	Timepoint	Alu/Alu blister	PVC-PEPVDC/Alu blister	HDPE bottle
5 °C	3	0.20	0.19	0.20
25 °C/60% RH	3	0.20	0.20	0.19
	6	0.20	0.20	0.20
	9	0.20	0.19	0.19
	12	0.20	0.22	0.20
	24	0.21	0.25	0.23
	36	0.24	0.30	0.27
40 °C/75% RH	3	0.25	0.33	0.26
	6	0.37	0.74	0.47

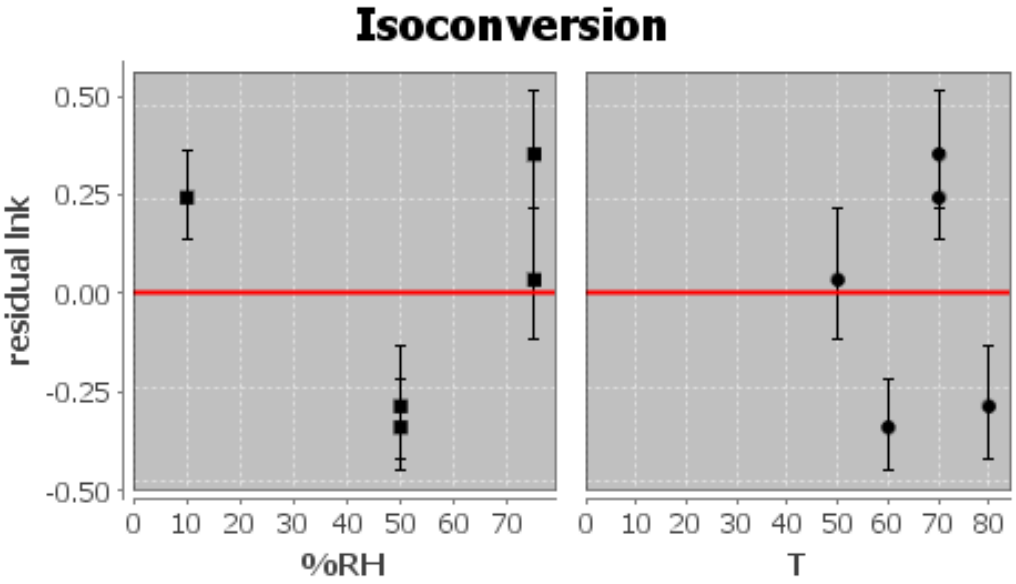
- ✓ 6 months data no packaging!
- ✓ No sufficient data at 5°C
- ✓ No time to screen other packaging

ASAP results for 5mg capsule

Sample	RRT0.81	API	RRT1.04	RRT1.32	RRT1.38	RRT1.50
Time zero	<0.05	99.24	0.09	0.15	0.06	0.17
3d 50C/75RH	0.07	99.36	0.13	0.16	0.06	0.18
7d 50C/75RH	0.05	99.08	0.09	0.04	0.06	0.2
14d 50C/75RH	0.15	99.08	0.1	0.05	0.06	0.24
3d 60C/50RH	0.1	99.4	0.1	0.15	0.06	0.18
7d 60C/50RH	<0.05	99.3	0.08	0.15	0.06	0.2
7d 60C/50RH dup	0.05	99.45	0.09	0.16	0.06	0.19
14d 60C/50RH	0.17	99.06	0.12	0.15	0.06	0.22
3d 70C/10RH	0.05	99.1	0.09	0.16	0.06	0.21
7d 70C/10RH	0.06	99.18	0.11	0.16	0.07	0.27
7d 70C/10RH dup	<0.05	99.4	<0.05	0.15	0.06	0.27
14d 70C/10RH	0.1	98.48	0.08	0.15	0.06	0.47
1d 70C/75RH	0.06	99.3	<0.05	0.16	0.05	0.2
3d 70C/75RH	0.05	99.11	0.1	0.15	0.06	0.35
3d 70C/75RH	0.06	99.19	0.09	0.15	0.06	0.37
7d 70C/75RH	0.09	99.02	0.08	0.15	0.06	0.48
14d 70C/75RH	0.16	98.22	0.1	0.15	0.05	0.82
1d 80C/50RH	0.05	99.3	0.08	0.17	0.05	0.23
3d 80C/50RH	0.12	98.89	0.08	0.18	0.06	0.26
7d 80C/50RH	0.05	99.25	<0.05	0.14	0.05	0.39
14d 80C/50RH	<0.05	98.95	<0.05	0.14	0.05	0.46

ASAP study open dish study: Arrhenius parameters and predictions

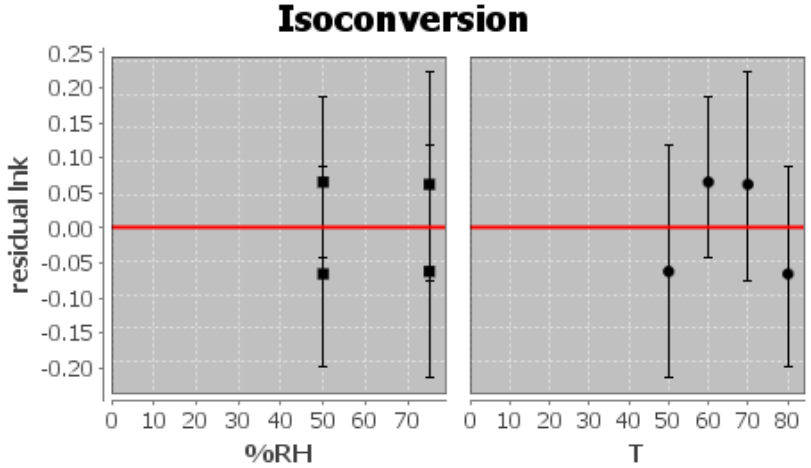
Parameters	All conditions
Ln A	33.8
Ea	25.15
B	0.017
R^2	0.82



Bad fit between conditions

ASAP study open dish study: Arrhenius parameters and predictions

Parameters	With 10%RH	Without 10%RH	
Ln A	33.8	35.6	
Ea	25.15	27.4	
B	0.017	**0.042**	DP is humidity sensitive
R^2	0.82	0.99	



better fit between conditions without 10%RH

=> Further investigation demonstrated a lost of constitutive water ~15%RH

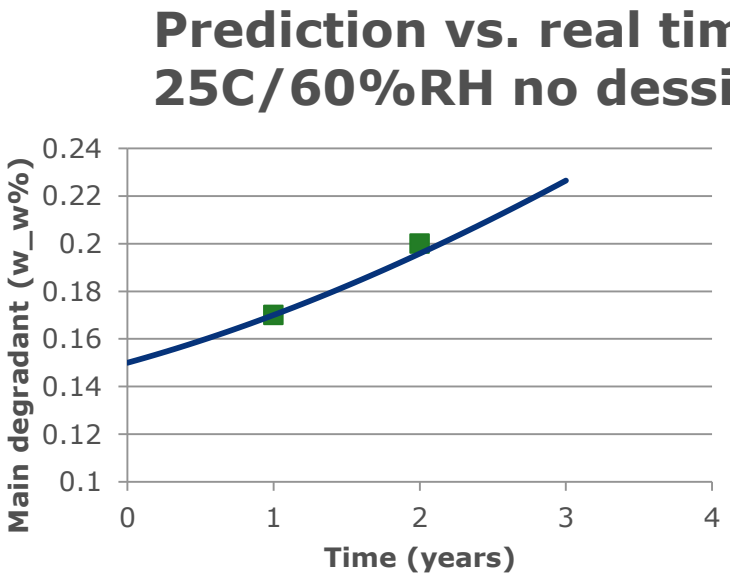
ASAP study open dish study: Shelf life prediction

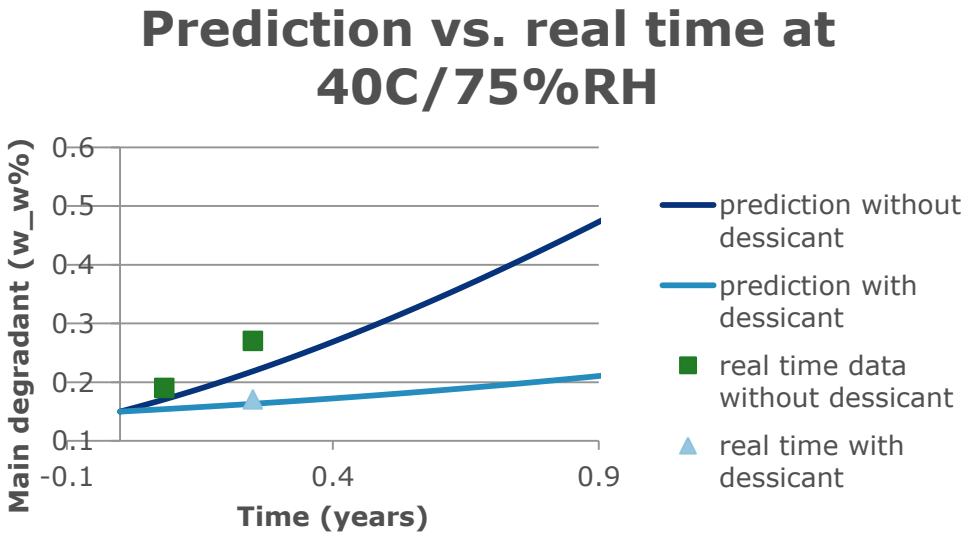
Package Type		75cc HDPE bottle 25 capsules/bottle	
Predictions		5 mg capsules	
		25°C/60%RH	40°C/75%RH
shelf-life (years)	Prediction	> 3y	0.6
	95% confidence	2.5	0.37
shelf-life (years) + 2g silica	Prediction	> 3y	1.3
	95% confidence	> 3y	0.76

IND-CTA protocol 5 and 10 mg

Storage Condition	Storage Time (Months)	API	DEG Spec. 0.30%
5 mg HDPE bottle	Initial	102.9	0.18
5 °C	1	105.2	0.17
25 °C/60% RH	12	97.7	0.17
	24	97.1	0.20
40 °C/75% RH	1	102.0	0.19
	3	101.5	0.27
50 °C	1	102.3	0.30
5 mg HDPE bottle +2g desiccant	Initial	102.9	0.18
25 °C/60% RH	24	98.8	0.17
40 °C/75% RH	3	100.0	0.19

Comparison graphs real time vs predictions





ICH vs. ASAP methodology in Small Molecules

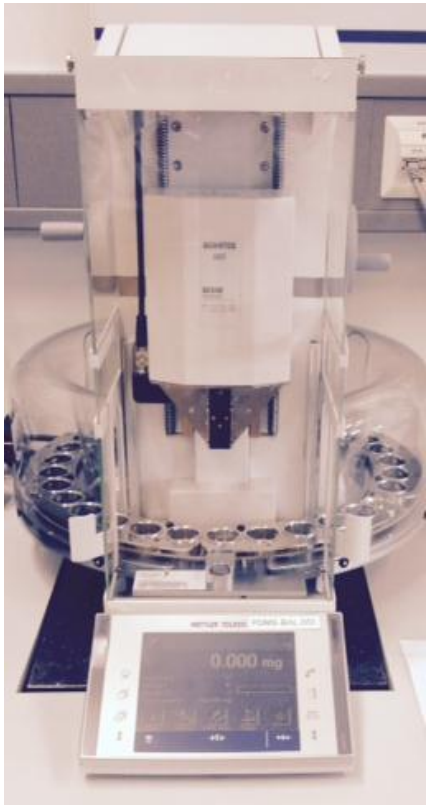
ICH	ASAP
Long-term: 5%C, 25°C/60%RH, **Accelerated conditions:** 40°C/75%RH, 4 packaging 6 months	**Broader range of conditions:** (40°C to 80°C, 10 to 75%RH) Open dish studies 1month
• 120 samples for assay purity • 120 samples for water **=> No packaging can be selected!**	•80 samples for assay purity but done in 1 time point •3 DVS for water simulation
Disso information in addition	**Can be compensated by humidity screen**

Lab automation

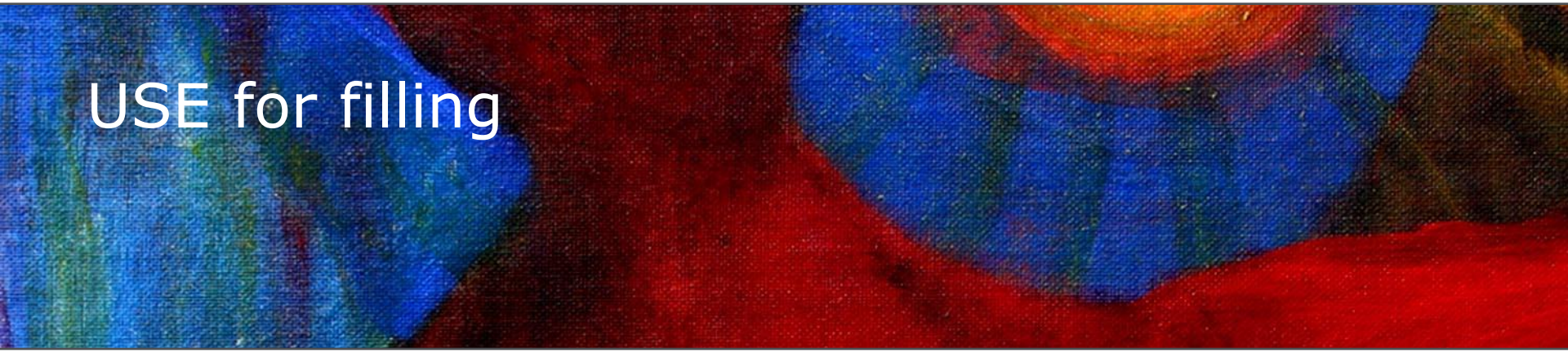
Automation tool to optimize resource

Automated sample preparation

- ✓ More samples in 1 time
- ✓ Development and GMP (SOP)
- ✓ Optimize resources



Automated balance


USE for filling

Use in filing

ASAP is not just a development/screening tool it can be successfully used in filling to support shelf life

- For phase I shelf life application only ASAP data: 5 times without any questions
- For phase IIa shelf life application with 1 or 3 months ICH
- As supportive tool for scientific justification of specification in late phase

ASAP use and potential

- Shorten Drug Product development
- Improve scientific understanding
- Packaging prediction to minimize screening study
- Support shelf life in filling for early phase

- **Gain time by increasing product knowledge!**

Ana Lucia Llano Arango, Geert Van Nyen, Katrien Backx, Christine Schroyen…..