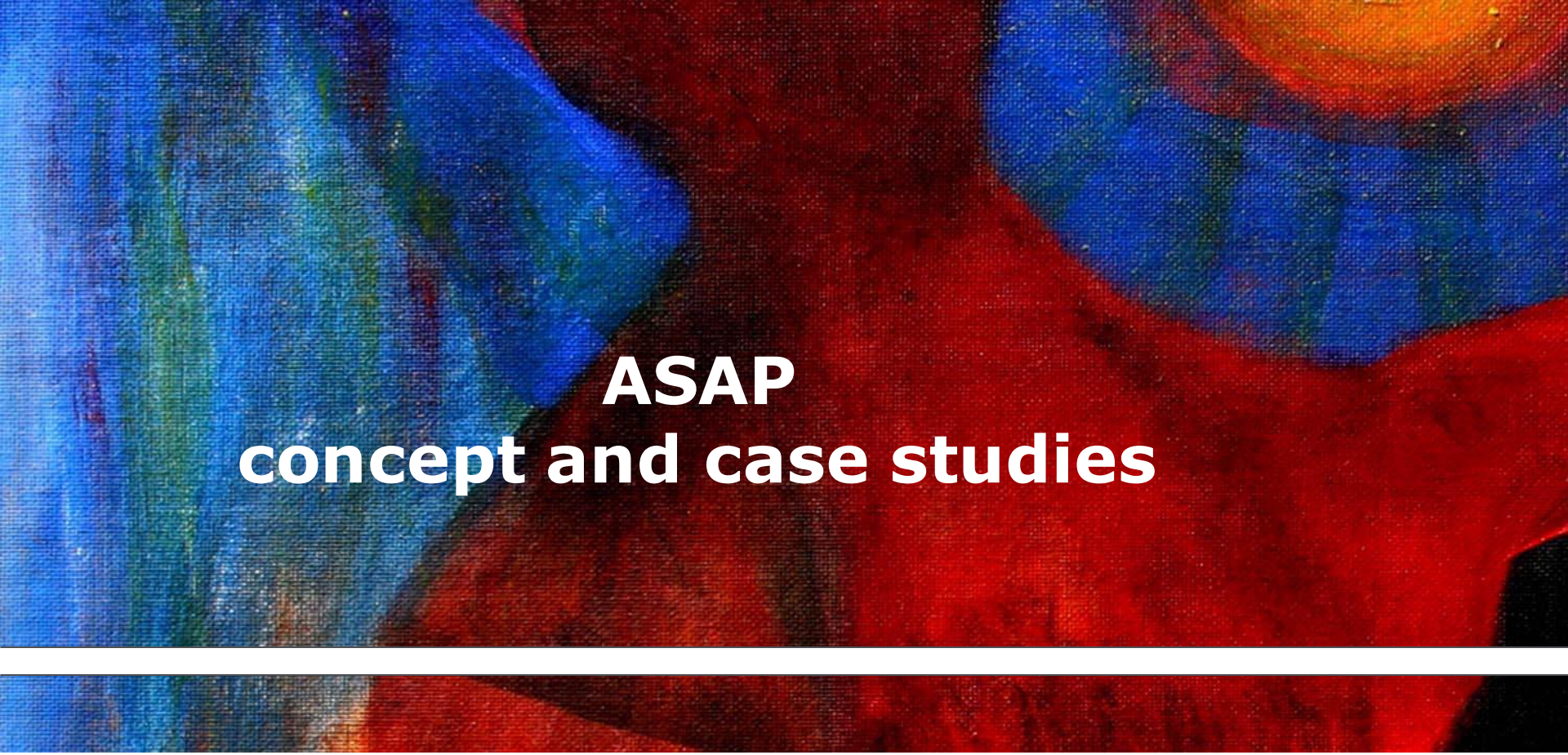

ASAP
concept and case studies

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Stability Testing for Pharmaceuticals

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Background:
Traditional Approaches to Stability Studies (ICH)

1. Long-term –e.g. 25°C/60%RH, 30°C/75%RH etc.

Little or no degradation after 3 weeks or 6 weeks; extrapolation of 3 or 6 wk data to estimate shelf life is prone to error

2. Accelerated conditions: e.g. 40°C/75%RH, 50°C etc.

–Uncertain relationship to long-term stability performance (e.g. are these conditions 2, 4 or 10-fold accelerations, are they representative at all to long term?)

–Have questionable reliability: conclusions sometimes contradictory (which condition is most relevant to long-term?); sometimes have been found to be misleading in retrospect

ASAP vs. ICH

- Isoconversion : aim to degrade sample to the specification level for all conditions avoid kinetic assumption
- Using Humidity corrected Arrhenius equation: open dish studies
- Statistical approach :
  - analyze everything at the same time (minimize analytical variation)
  - Broader range of conditions (temperature and humidity)

Humidity Corrected Arrhenius Equation

collision frequency

humidity sensitivity factor

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

1/(isoconversion time)

activation energy

equilibrium relative humidity

ASAP Protocol

- Conditions and durations chosen for their practicality and to provide about ~0.5% degradation based on typical Ln A, Ea and B values
- 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	10	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- Limitations

•ASAP can not be expected to predict the stability of parameters such as:

– *Dissolution / disintegration performance*

– *Appearance*

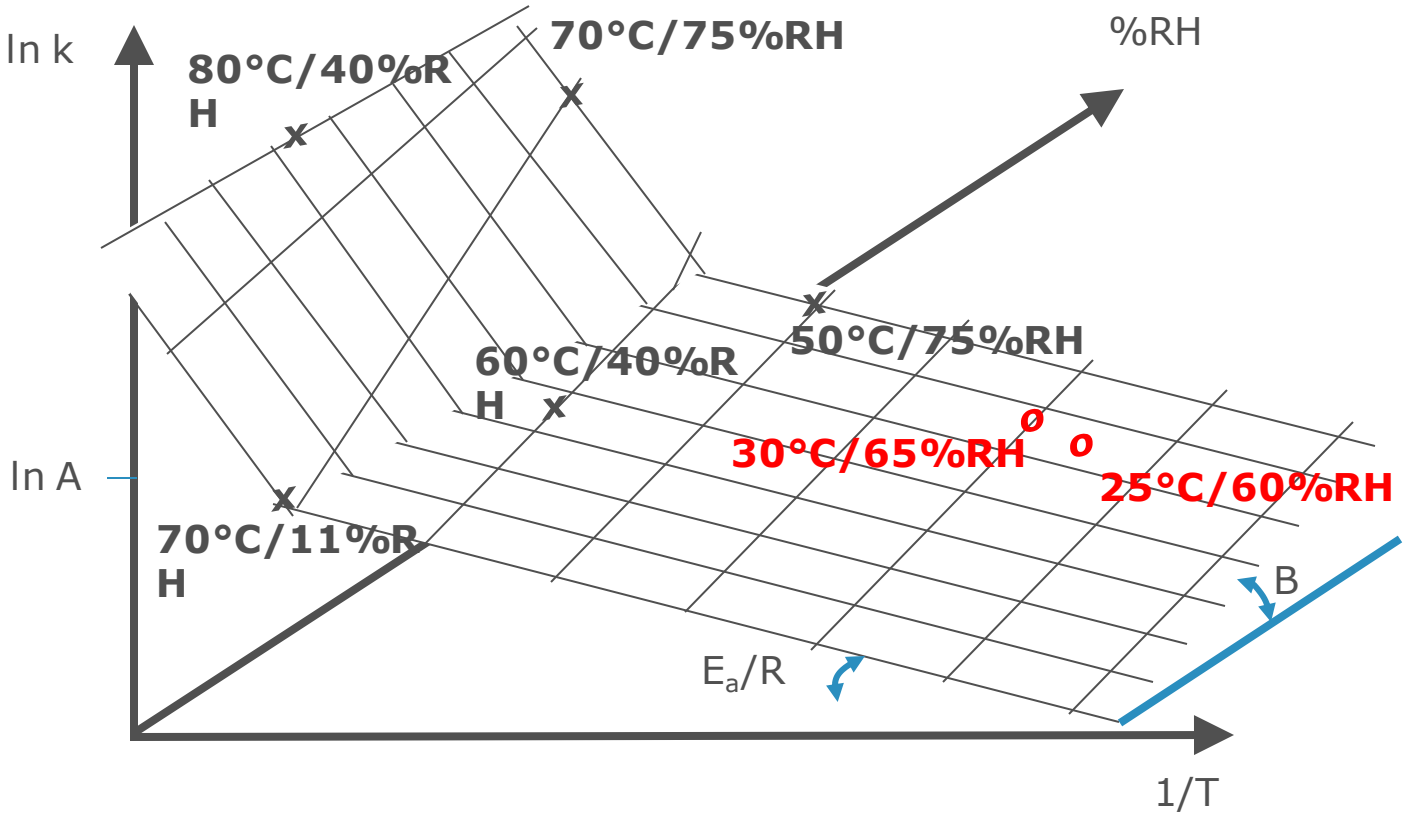
- Physical changes

- Large Molecule

• ***You need a good tool to interpret data!***

•***ASAP does not work in some cases!***

Possible Failure Mode: Form/Phase change caused by T/RH: melts, glass transitions, anhydrate/hydrate formation



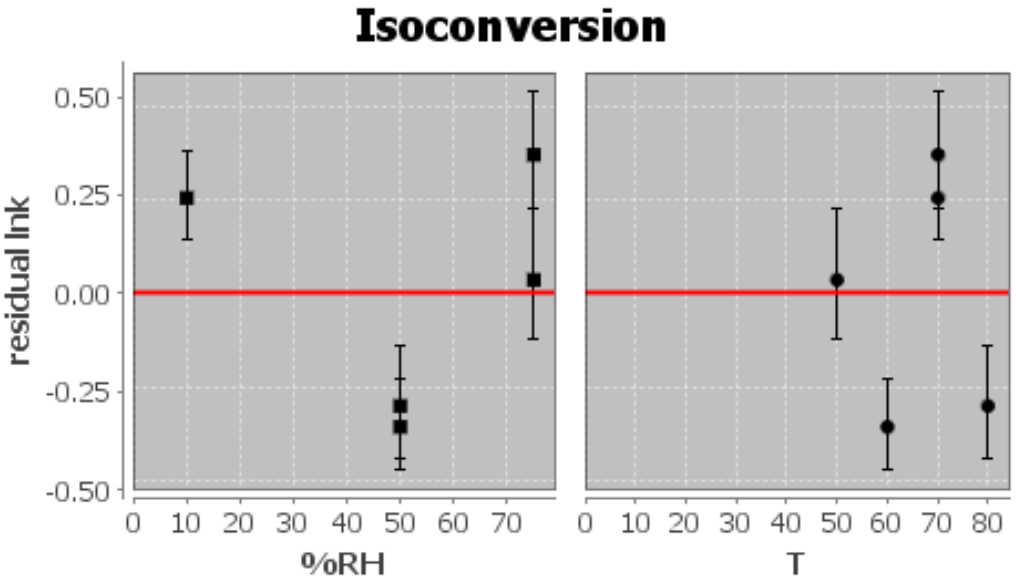
Case Study 1:
Shelf life prediction
Packaging recommendations

ASAP results for 5mg capsule

Sample Name	RRT0.81	API	RRT1.32	RRT1.38	RRT1.50
Initial		99.46	0.14	0.06	0.17
3d 50°C/75RH	0.06	99.29	0.15	0.06	0.22
7d 50°C/75RH	0.13	99.06	0.14	0.06	0.29
14d 50°C/75RH	0.10	98.66	0.20	0.05	0.36
3d 60°C/50RH	0.05	99.33	0.14	0.06	0.23
7d 60°C/50RH	0.13	99.00	0.15	0.05	0.28
7d 60°C/50RH duplicate	0.04	99.12	0.14	0.05	0.28
14d 60°C/50RH	0.22	98.78	0.15	0.06	0.37
3d 70°C/10RH	0.04	99.08	0.14	0.06	0.39
7d 70°C/10RH		98.78	0.14	0.06	0.65
7d 70°C/10RH duplicate	0.61	98.13	0.14	0.06	0.59
14d 70°C/10RH		96.86	0.13	0.05	2.07
1d 70°C/75RH		99.34	0.14	0.06	0.32
3d 70°C/75RH	0.04	98.35	0.14	0.05	0.87
3d 70°C/75RH duplicate	0.05	98.45	0.14	0.05	0.83
7d 70°C/75RH	0.04	97.86	0.15	0.05	1.27
14d 70°C/75RH	0.04	96.41	0.13	0.05	2.32
1d 80°C/50RH	0.04	99.35	0.15	0.05	0.27
3d 80°C/50RH	0.06	98.77	0.16	0.06	0.62
7d 80°C/50RH		97.57	0.15		1.3
14d 80°C/50RH	0.04	96.68	0.15	0.05	1.96

ASAP study open dish study: Arrhenius parameters and predictions

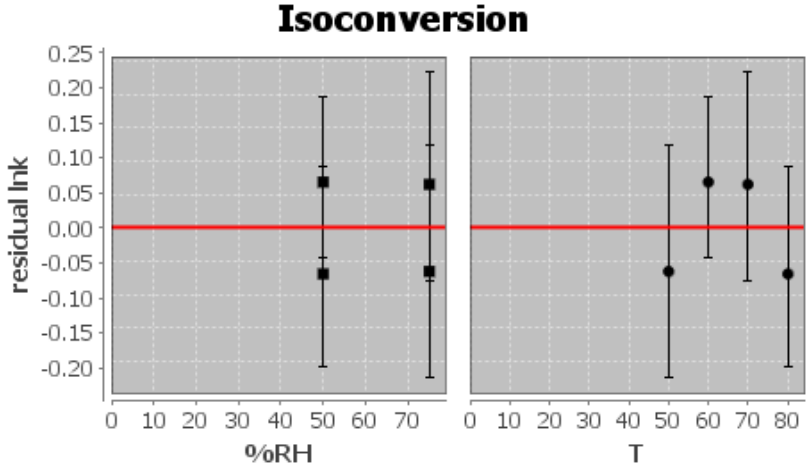
Parameters	All conditions
Ln A	33.8
Ea	25.15
B	0.017
R^2	0.82



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

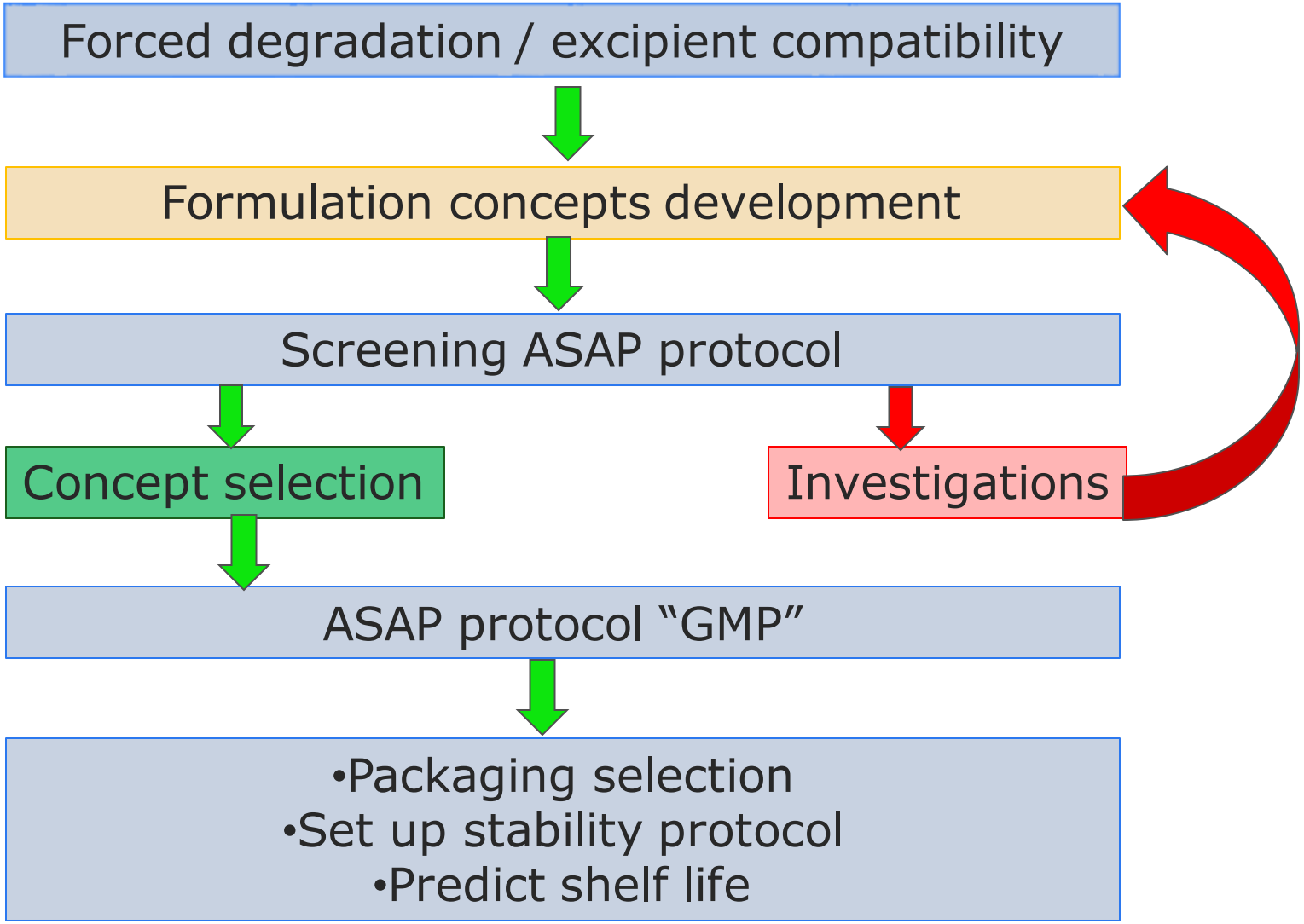
Package Type		75cc HDPE bottle 25 capsules/bottle			
Predictions		5 mg capsules		10 mg capsules	
		25°C/60%RH	40°C/75%RH	25°C/60%RH	40°C/75%RH
shelf-life (years)	Prediction (50%)	3	0.5	3.6	0.6
	99% confidence	1.7	--	1.6	0.3
shelf-life (years) + 2g silica	Prediction (50%)	6.8	1	11.4	1.8
	99% confidence	3.9	0.6	6.8	1.2

IND-CTA protocol 5 and 10 mg

Storage Condition	Storage Time (Months)	API	DEG Spec. 0.30%	Total
5 mg HDPE bottle	Initial	102.9	0.18	0.40
5 °C	1	105.2	0.17	0.30
25 °C/60% RH	1	103.2	0.17	0.30
	3	100.0	0.16	0.25
40 °C/75% RH	1	102.0	0.19	0.32
	3	101.5	0.27	0.41
50 °C	1	102.3	0.30	0.43
10 mg HDPE bottle	Initial	102.1	0.18	0.40
40 °C/75% RH	1	97.4	0.15	0.28
	3	100.1	0.18	0.26
50 °C	1	100.8	0.18	0.50
5 mg HDPE bottle +2g desiccant	Initial	102.9	0.18	0.40
25 °C/60% RH	3	102.2	0.18	0.31
40 °C/75% RH	3	100.0	0.18	0.27

Case Study 2:
Capsules formulation development

DP development flow



Excipient compatibility: using DoE

- 4 blocks of 24 runs (evaluation of T and %RH)
- identification of 3 degradants (LC/MS identification)

- Advices given to DPD team:
  - Fillers :DCP ~ Mannitol ~ Lactose > MCC
  - Favorable excipients: Mg stearate and SLS
  - Aerosil increase degradation

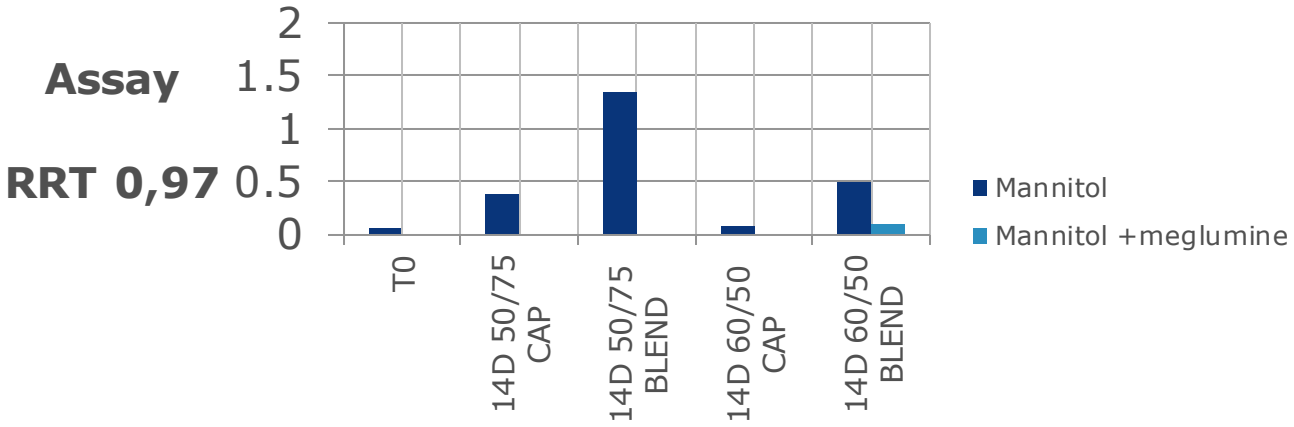
ASAP screening of capsules concept

- Major degradation especially for RRT0.97
- Variation between sample due to HPLC method
- Strong variation between closed capsules and blends

- RRT0.97 correspond to addition of formaldehyde
- HPLC method? Suggest to change solvent
- Formaldehyde source? In API, excipient and/or contamination

Last formulation screening

- **Formulation changes**: Addition of formaldehyde scavenger: Meglumine
- **Process changes**: Change order of addition of excipient
- **Method changes**: Change sample prep solvent to DMF/ACN/water



Last concept with meglumine showed **no degradation in capsule** after 2 weeks open dish

Out-come

•Identification of degradation profile in early phase: Major degradation especially for RRT0.97 initiate toxicology tests (spec. 0.7%)

•Modification of HPLC method

•6 months time frame screen 6 blocks 25 concepts (2 types of capsules)

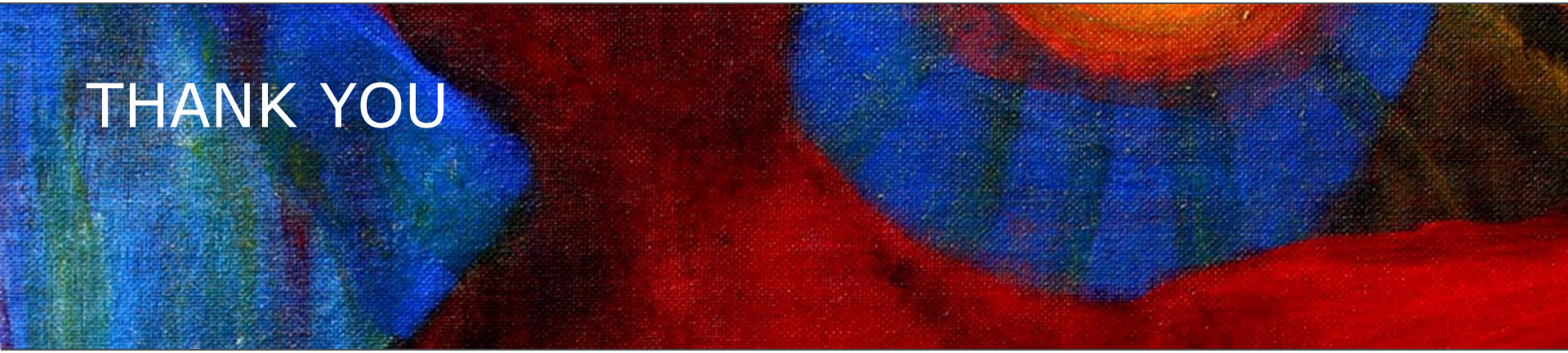
•Working in parallel (stability, characterization, process)

Applications of ASAP

- Shelf-life predictions for Drug Substances and Drug Product
- Support filling of Drug Substances and starting materials
- Shorten Drug Product development and improve scientific understanding
- Packaging prediction to minimize screening study
- Evaluation of process robustness

ASAP: collaboration between departments

- Stability group:
  - Accurate stability data from open dish studies
- Pharmaceutical Science:
  - Physical stability information to adapt conditions
  - GAB parameters from DVS of excipient or DP
  - Automation with CM3 to reduce workload
- Drug Product Development:
  - Concept preparation
  - Feed back on other parameters of the DP to find the optimal formulation (flowability….)
- Packaging group:
  - MVTR to build a database
  - Support for packaging selection


THANK YOU