Application of ASAP in Early API and Formulation Development

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FDA requirement on stability testing for clinical development

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Expiration Dating and Stability testing for human Drug Products, 10/18/85

- When accelerated stability studies are performed, one batch may be adequate in order to establish a tentative expiration date. This acceptable since it is not the purpose of an accelerated test to determine batch uniformity but rather to test for kinetic degradation.

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs

- Although stability data are required in all phases of the IND,...., if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.

cGMP for Phase 1 Investigational Drugs

- We recommend initiation of a stability study using representative samples of the phase 1 investigational drug to monitor the stability and quality of the phase 1 investigational drug during the clinical trial (i.e., date of manufacture through date of last administration).

Scope of stability testing during early clinical development

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Stability assessment of candidates, salt and form selection

Stability indicating methods development

DS

Stability of test article, retest period of reference standard and clinical drug substance, and storage conditions and packages selection for bulk API, ID of degradation products

API lot to lot stability and process changes assessment

Stability assessment of mutagenic degradation product

Qualify clinical supply during clinical trial

Stability evaluation of prototype formulations

Drug – excipient compatibility studies

Evaluation of formulation manufacturing process

DP

Establishment and confirmation of use periods, packaging and storage conditions of clinical supplies (trial formulations), ID of degradation products

Qualify clinical supply during clinical trial

Stability strategy for early clinical stability testing

- Turnaround quickly for fast decision making
- Flexible for different applications
- Accelerate the timeline to FIH

- Save precious materials and resources
- Reduce unnecessary redundancies

Ensure the quality of early clinical stability testing by using both ICH and science and risk based non-ICH approaches for the right purposes.

Stability approaches for early clinical development

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	Storage Conditions	Duration	Application
ICH	25C/60%RH w/packaging 40C/75%RH w/packaging	≥12 M 6 M	concurrent stability, expiry, physical/chemical stability
Modified ICH	25C/60%RH w/packaging	annual	concurrent
	25C/60%RH w/packaging 40C/75%RH w/packaging	≥3 M ≥3 M	expiry, physical/chemical stability
	25C/60%RH/open dish 40C/75%RH/open dish	≥3 M ≥3 M	expiry, physical/chemical stability
	25C/variable %RH/open dish 40C/variable %RH/open dish	≥3 M ≥3 M	expiry, physical/chemical stability
	40C/75%RH w/o packaging	≤3 M	Expiry, physical/chemical stability
Accelerated testing	High temperature/w/o %RH	≤3 M	Initial expiry, chemical stability
	ASAP (>4 T/RH conditions)	1-4 W	Initial expiry, chemical stability
	Other non-ICH approaches		

Use of high temperature w/o moisture approach for drug substance stability testing

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An example DS stability strategy up to phase 2a

DS Batch	ICH stability study	Bridging stability study
4 week tox batch		70C/75%RH, 3 week (initial retest period)*
First clinical batch	Concurrent, Acc./long term	70C/75%RH, 3week
Second clinical batch	Concurrent, Long term annual pull up to 3 years	70C/75%RH, 3 week

*:

- 15 Months if no degradation (~70%)
- 15 months if degradation < 0.3% (~10-20%)
- Perform additional study if degradation >0.3% (~10-20%)
- Estimation is based on the principle of Arrhenius relationship ("2 for 10"/13kcal/mol), and is accepted by BfArM and FDA.

Example 1: Use of high temperature w/o moisture for stability risk assessment

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Batch	C. Solvent	Residual EtOH	Residual IPA	water	Degradation
4 week tox batch	IPA/ heptane	NA	1.59%	0.26	70/75%RH (open) Deg 1 0.43%/1wk 0.66%/2 wk 0.80%/3wk Deg 2 0.06%/2wk 0.08%/3wk
First clinical batch	EtOH/ heptane	0.10%	0.04%	0.08	6M 40C/75%RH No change
Reference Std batch	EtOH/ heptane	0.18%	0.03%	0.89%	12 M ambient Deg 1: No change Deg 2: 0.70%
Parent batch of second clinical batch	EtOH/ heptane	0.10%	0.36%	0.69%	3wk 70C/75%RH(closed) Deg 1: no change Deg 2: 4.2%

Example 1: Use of high temperature w/o moisture for stability risk assessment

t=0 t=3wk closed vial t=3wk open vial

Use of ASAP (Accelerated Stability Assessment Program) in early clinical development

	DS	DP
High Temperature /w/o Moisture	• Useful for most of the early clinical purposes • Possible for risk based and qualitative initial retest period setting of ~70-80% of drug substances	• Mostly used for stress testing and non-expiry stability testing • typically not used for direct expiry dating
ASAP	• Can be quantitative • Isoconversional • Fit the early clinical purposes for most candidates	• Can be quantitative • Isoconversional • Fit the early clinical purposes for most of SOF products

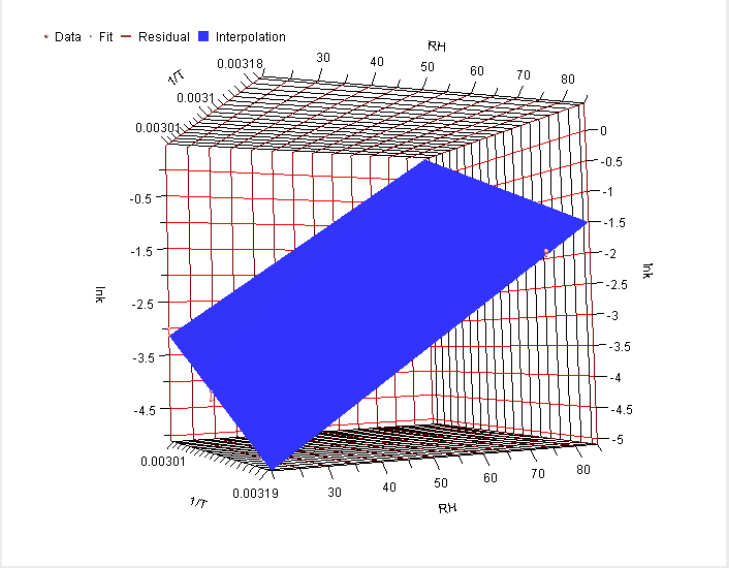
ASAP model evaluation: Drug M tablets

	Days	T(C)	%RH	RRT0.24 net increase	lnk
Scout run	3	60	20	0.148	-3.00916
	3	40	75	0.41	-1.99021
	3	50	20	0.044	-4.22218
	3	60	85	4.439	0.391817
Second run	4	60	**20**	0.174	**-3.13499**
	2	40	**75**	0.270	**-2.00248**
	3	30	**75**	0.113	**-3.27898**
	12	50	**20**	0.139	**-4.45819**

Modeling using XLfit or SigmaPlot

$y = ax + by + cz$

(lnk = lnA + Ea/RT + B(RH))



ASAP model evaluation: Drug M tablets

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First round, 4 conditions

	Name	Value		95% Confidence Limits	
1	a	26.34089375	78.25956088	-25.5777734	+/-197%
2	b	-10183.5666	6836.701599	-27203.8349	+/-167%
3	c	0.055163437	0.099865652	0.010461223	+/-82%

Second round, 4 conditions

1	a	34.5973146	74.51748377	-5.32285456	+/-115%
2	b	-13036.0804	364.0078838	-26436.1688	+/-103%
3	c	0.067973985	0.121978384	0.013969586	+/-79%

Second round, 5 conditions

1	a	27.32809632	38.62238034	16.0338123	+/-40%
2	b	-10584.8304	-6871.35056	-14298.3103	+/-35%
3	c	0.058074196	0.072892209	0.043256182	+/-26%

All 8 data set (processed on July 8, 2011)

1	a	27.84895407	33.31699926	22.38090888	+/-19%
2	b	-10722.1014	-8914.44655	-12529.7563	+/-17%
3	c	0.057406488	0.063864703	0.050948272	+/-11%

7 data set (processed on July 8, 2011)

1	a	34.49394096	41.39528577	27.59259616	+/-20%
2	b	-12958.6009	-10646.7512	-15270.4505	+/-18%
3	c	0.065852122	0.074462645	0.057241599	+/-14%

ASAP model evaluation: Montelukast tablets

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- First round, 4 conditions
  - **Lnk = 26.34 -10183.6 * 1/T + 0.055 (RH)**
  - t25/60 = 18.6 days
  - t25/20 = 168 days
- Second round, 4 conditions
  - **Lnk = 34.69 -13067.5 * 1/T + 0.068 (RH)**
  - t25/60 = 32 days
  - t25/20 = 488 days
  - T25/10 = 964days = 2.64 years
- Second, 5 conditions
  - **Lnk = 27.33 -10584 * 1/T + 0.058 (RH)**
  - t25/60 = 22 days
  - t25/20 = 225 days
- 8 conditions (processed on July 8, 2011)
  - **Lnk = 27.85 -10722 * 1/T + 0.057 (RH)**
  - t25/60 = 22 days
  - t25/20 = 217 days
- 7 conditions (processed on July 8, 2011)
  - **Lnk = 34.49 - 12958 * 1/T + 0.066**
  - t25/60 = 31 days
  - t25/20 = 430 days
  - T25/10 = 832 days

Use ASAP for assessment of batch variability of drug substances

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	DS 1	DS 2	DS 3
Batch 1	1.1 years	1.1 years	No degradation
Batch 2	3.5 years	2.4 years	No degradation
Batch 3	12.5 years	-	No degradation
Batch stability	different	different	No difference

ASAP is sensitive to anomalies

Use ASAP to aid understanding of degradation mechanism and risk assessment

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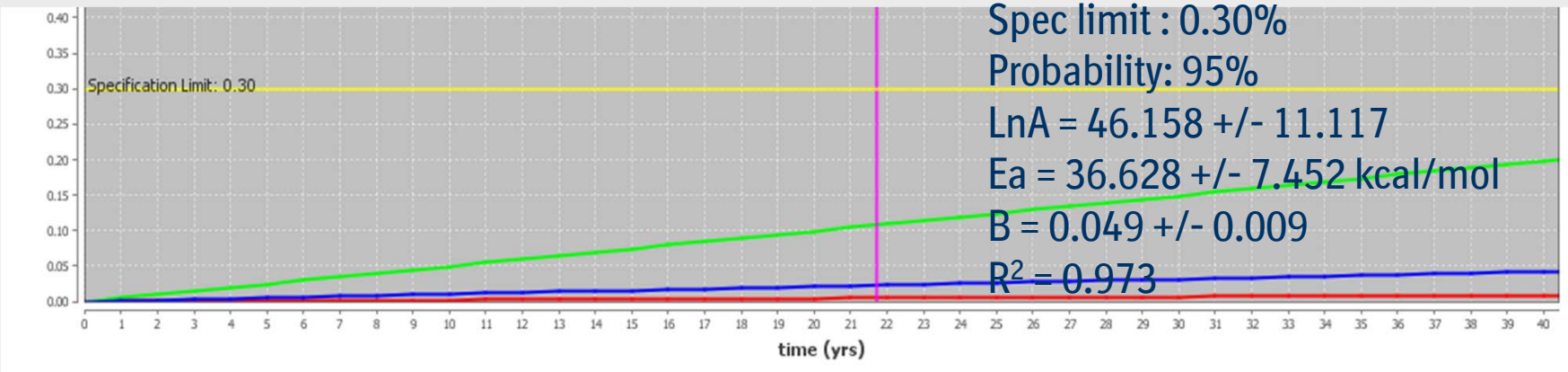
- Unknown RRT 0.49 exceeded the acceptance criteria under high T accelerated testing, hence an additional study was warranted to estimate the retest period
- RRT 0.49 appears to be formed from high temperature with high humidity from the degradation of RRT 0.66 and RRT 0.74, instead of API
- ASAP modelling suggested that the likelihood of formation at 25C is low

RRT	Initial	60C/50%RH 3 weeks	60C/75%RH 3 weeks	70C/11%RH 2 weeks	70C/11%RH 3 weeks	70C/75%RH 2 weeks	70C/75%RH 3 weeks	70C/75%RH 5 weeks
0.49	---	---	0.11	---	---	0.32	0.33	0.33
0.66	0.16	0.15	0.08	0.16	0.16	---	---	---
0.74	0.21	0.21	0.18	0.22	0.21	---	---	---



Use ASAP for assessment of potential drug substance physical form conversion

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Sample Info	Storage	% Form I	% Form II
Batch 2 (un-milled)	Control	ND	Form II
	70°C/75% RH	NC	NC
	70°C/11% RH	NC	NC
Batch 2 (milled)	Control	ND	Form II
	70°C/75% RH	NC	NC
	70°C/11% RH	NC	NC
Batch 3 (un-milled, mixture of form 1and 2)	Control	Mixture	Mixture
	70°C/75% RH	NC	NC
	70°C/11% RH	NC	NC

ND = None Detected, NC = No Change; test performed by ssNMR

Conclusion: both forms appeared stable in solid state

Use ASAP for assessment of drug substance chemical stability of different physical form stability

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%degradation under ASAP conditions

	T = 0	60°C/75%RH 2 Weeks	70°C/50%RH 1 Week	70°C/75%RH 5 Days	80°C/20%RH 4 Days
Form 1	0.12	1.0	1.0	1.3	0.88
Form 2	0.03	1.53	0.98	2.2	0.73

Form 1: Lnk = 40.39 -29.86/RT + 0.026 (RH), **25°C/60%RH expiry: 4 years**

Form 2: Lnk = 43.74 -32.52/RT + 0.042 (RH), **25°C/60%RH expiry: 6 years**

(predicted using ASAPprime for open dish with 1% acceptable limit)

Use of ASAP for prediction of drug substance retest period

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40C/75%RH

	Time Zero	Double PE Bags in fiber drum			Double PE Bags sealed in Aluminum pouch in fiber drum		
		1 M	3 M	6 M	1 M	3 M	6 M
Deg 1	0.12	0.31	0.61	0.88	0.19	0.43	0.58
ASAP prediction		0.23±0.10	0.44±0.32	0.77±0.60	0.15±0.08	0.23±0.18	0.35±0.34

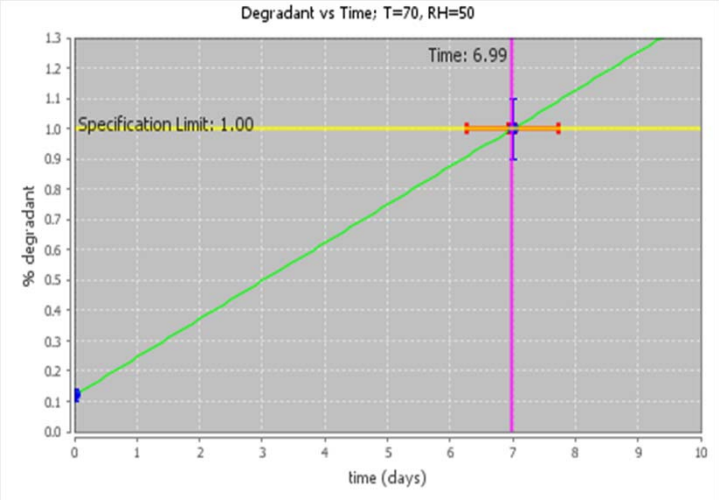
25C/60%RH

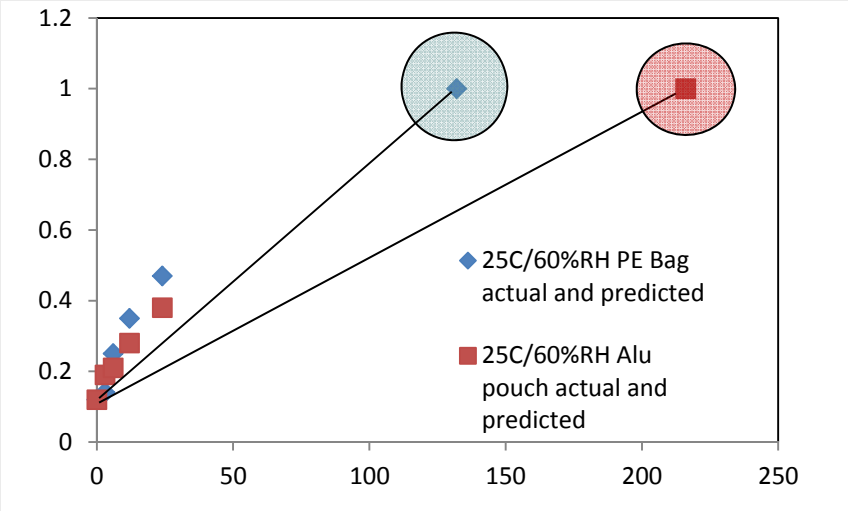
	Time Zero	Double PE Bags in fiber drum				Double PE Bags sealed in Aluminum pouch in fiber drum			
		3 M	6 M	12 M	24 M	3 M	6 M	12 M	24 M
Deg 1	0.12	0.14	0.25	0.35	0.47	0.19	0.21	0.28	0.38
ASAP prediction		0.14±0.04	0.16±0.08	0.20±0.16	0.28±0.26	0.13±0.03	0.14±0.06	0.16±0.12	0.21±0.22
ASAP+3M 40C/75%RH Prediction		0.16±0.03	0.20±0.05	0.28±0.09	0.44±0.17				

Long term Stability data vs. ASAP Prediction

Too few (4) ASAP data points can be a factor impacting the accuracy of the prediction

ASAP prediction is based on isoconversion, prediction at lower level can be less accurate





Use of ASAP for SOF prototype formulation and packaging selection

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- Conventional excipient compatibility study failed to provide any insight in excipient selection due to severe degradation of all combinations
- 6 prototype formulations with 50% DL were made using a platform formulation

Package	F1	F2	F3	F4	F5	F6
HDPE bottle * (No desiccant)	~1 year**	1 year	1 year	5.8 years	4.5 years	4.8 years
HDPE bottle * (With desiccant)	~1 year	1.5 years	1.2 years	> 5 years	8.5 years	9 years
PP bottle * (No desiccant)	~1 year	~1 year	~ 0.7 year	3.5 years	3 years	3 years
PP bottle (With desiccant)	~1 year	> 1 year	1 year	~6 years	4.5 years	4.5 years
Alu-Alu blister	~1 year	1 year	9 months	~6 years	4.9 years	5 years

* 30 tablets per bottle (80 cc PP bottle and 60 cc HDPE bottle)
** predicted shelf life based on Specification level for degradation product at 5%

Use of ASAP for SOF prototype Comparison

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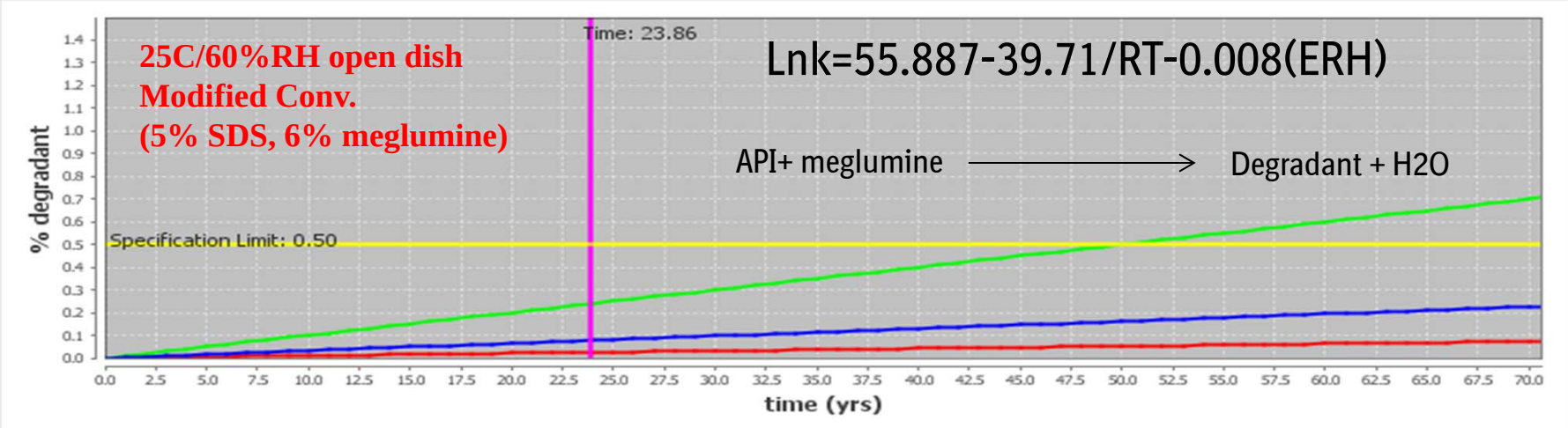
1 mg Tablets	RRT	% Degradant and Asssay (%w/w)				
		50°C/50%RH (14 days)	60°C/50%RH (14 days)	70°C/20%RH (14 days)	70°C/60%RH (14 days)	70°C/75%RH (3 days)
SE conventional	0.70	ND	ND	ND	ND	ND
SE Modified Conv. (5% SDS, 6% meglumine)	0.70	ND	0.24%	**0.95%**	0.56%	0.21%
SE Modified Conv. (3% meglumine)	0.70	ND	0.27%	**0.77%**	0.36%	ND
AN Conventional (platform dry granulation)	0.70	ND	ND	ND	ND	ND



Drug Product ASAP vs. Actual Stability Data

	P1 TFI (50mg)	P2 20/80mg	P3 TFI (10mg)	P4 TFI 25mg	P5 XP (1mg)	P6 10 mg
ASAP	1 year 95%P	no deg.	>20 year	no deg.	>24 years	> 15 year mean shelf life
25C/60%	12 M no deg.	12 M no deg.	18M no deg.	12 M no deg.	24M no deg.	6 M no deg
40C/75%	6M 0.15% (0.20)*	6 M no deg.	6 M no deg.	6 M no deg.	6 M no deg.	6 M no deg.

*: ASAP prediction

ASAP predicted that BI 1181181 tablets will have a relatively short shelf life, 40C/75%RH data inline with predicted value.

Most products were predicted to be stable by ASAP (no deg. or very lower level deg.), typically degradation is not expected at 25C/60%RH within two years.

Summary

- ASAP was implemented for both DS and DP in early clinical development for routine stability assessment and initial expiry dating
- Positive experiences have been gained so far

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