Jennifer Jacobs, *Stowaway*
Jennifer is a New York based artist living with Type 1 diabetes.

From powder for reconstitution to oral suspension

Dr. Ellen Verheyen | October 3rd 2017

Janssen Research and Development
Pharmaceutical Development and Manufacturing Sciences
Analytical Development- Clinical Release and Stability

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Background information

- Drug product profile: oral suspension
- Therapeutic area: infectious diseases and vaccines

Forced degradation study on drug substance

- **Significant hydrolytic degradation** under acidic and basic conditions;
- Moderate hydrolytic degradation under neutral conditions

→ Solutions and suspension should be stored refrigerated and are only stable for a limited time period

Background information

- Drug product → two-bottle approach

  Drug substance in dry powder blend & Solvent
  → Reconstitution prior to dosing
  → In use stability target: 14 days at room temperature (RT)

- Reconstituted suspension is surprisingly stable

  → No degradation observed after 6M storage at RT

New opportunity → **one-bottle approach**

Can the reconstituted suspension be considered as final drug product?

Risk based predictive stability - protocol

- Evaluate stability of reconstituted suspension with ASAP

  Can the reconstituted suspension be stored for > 24M ?

	Timepoints (days)						
T (˚C)	3	7	14	21	28	35	42
5 (control)							A*
25					A	A	A
30			A	A	A	A*	A
40	A	A	A	A	A*	A	A
50	A	A	A	A			
60	A	A	A				

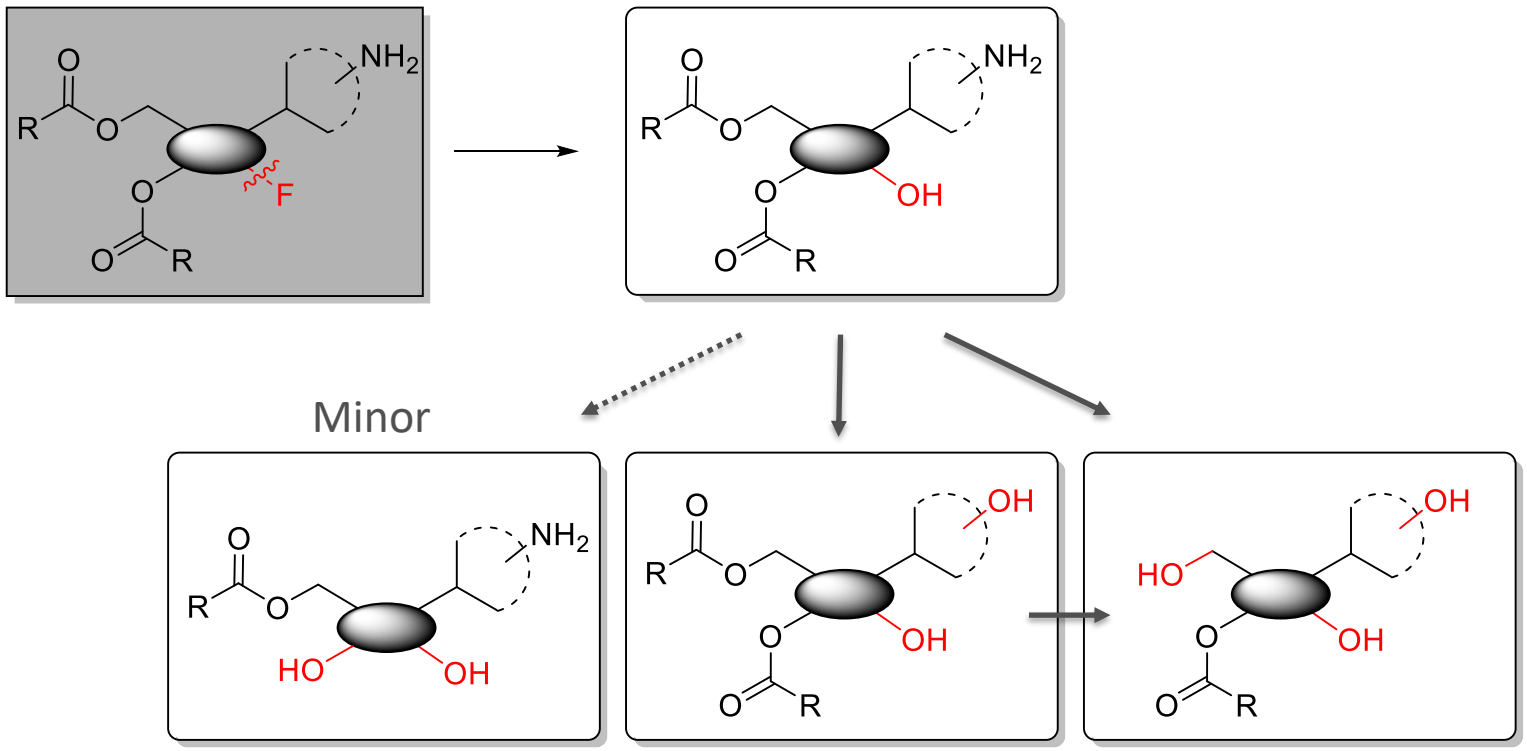
* Duplicates

Samples are put on conditions in a staggered fashion and removed from the stability chambers on the same time

Risk based predictive stability - results

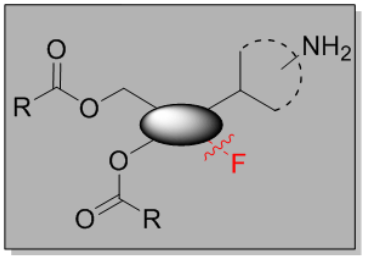
- UPLC analysis
- Degradant levels up to 0.30wt% in most extreme conditions
- Specifications limits to be determined
- Evaluate degradation kinetics using ASAP*prime*® software

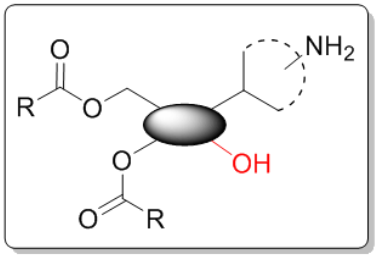
Hydrolytic degradation pathway

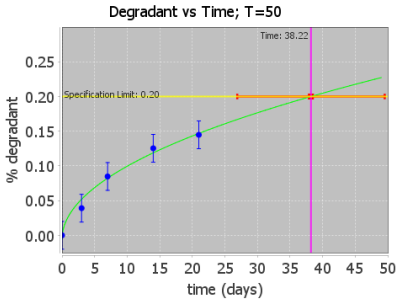


Secondary degradation → Challenge to identify Shelf Life limiting degradant

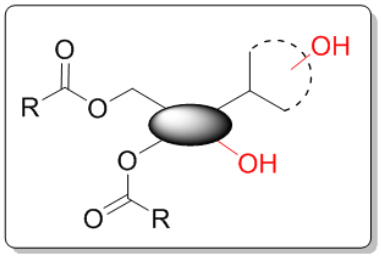
Hydrolytic degradation - Kinetics

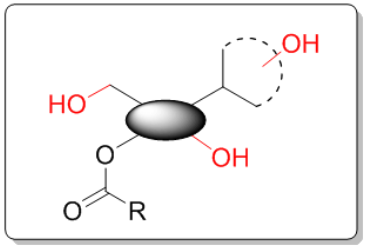


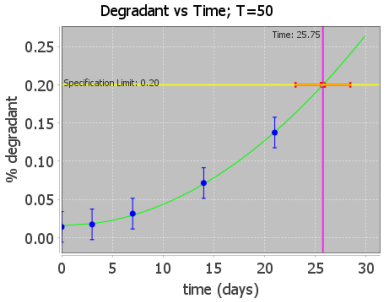




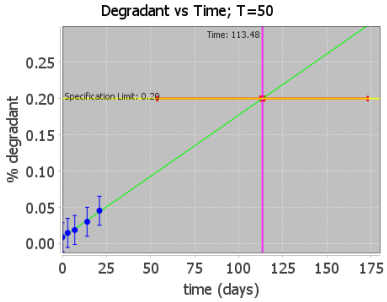
FIT – Diffusion		
lnA	67.1 ± 8.1	
Ea	46.5 ± 5.2	kcal/mol
R^2	0.999	
Q^2	0.994	







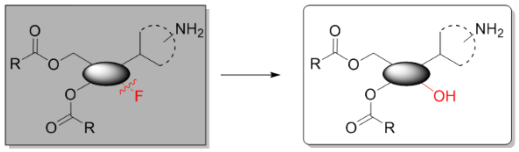
FIT - Avromi		
lnA	28.3 ± 6.8	
Ea	21.4 ± 4.4	kcal/mol
R^2	0.996	
Q^2	0.988	



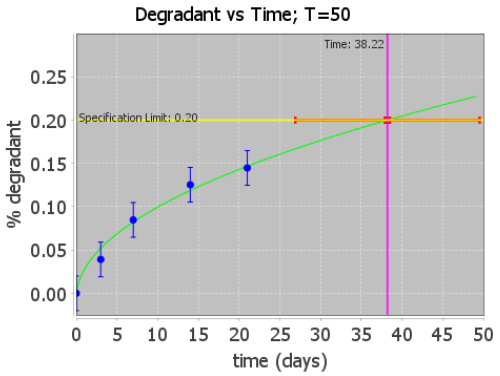
FIT - First order		
lnA	31.3 ± 7.7	
Ea	24.2 ± 4.9	kcal/mol
R^2	0.998	
Q^2	0.996	

Risk based Shelf–Life prediction

- Degradation kinetics are interconnected
  - Control primary degradation → control 2nd degradation
- Primary degradant → Diffusion → not Shelf-Life limiting

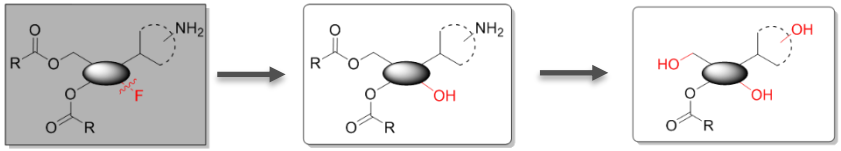


Potential Specification Limit		0.2%
5°C	Shelf Life (years)	>3
	Confidence for 2y	100%
25°C/60%RH	Shelf Life (years)	> 3
	Confidence for 2y	100%
30°C/75%RH	Shelf Life (years)	> 3
	Confidence for 2y	100%
40°C/75%RH	Shelf Life (years)	0.9
	Confidence for **6M**	96.7%

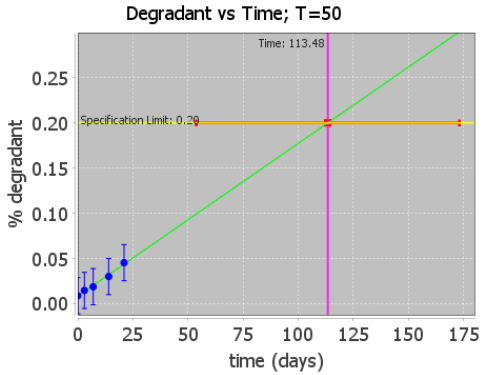


Risk based Shelf–Life prediction

- 2nd degradants → apparent Linear → not Shelf-Life limiting

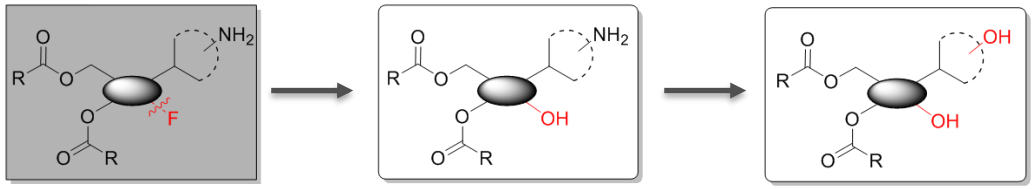


Potential Specification Limit		0.2 %	0.3%
5°C	Shelf Life (years)	>3	>3
	Confidence for 2y	99.9	100%
25°C/60%RH	Shelf Life (years)	>3	>3
	Confidence for 2y	96.0	99.0%
30°C/75%RH	Shelf Life (years)	>3	>3
	Confidence for 2y	86.6	96.2
40°C/75%RH	Shelf Life (years)	1.1	1.7
	Confidence for **6 M**	97.5%	99.9%



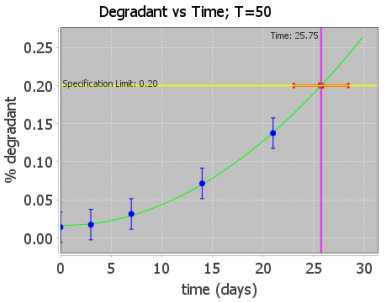
Risk based Shelf–Life prediction

- 2nd degradant



→ Avromi modelling → overestimation?

→ Hydrolysis → First order kinetics?



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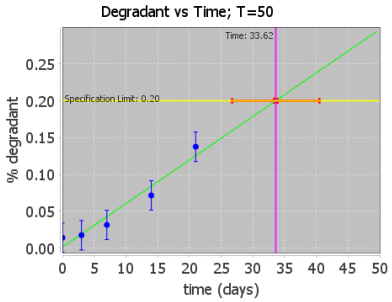


FIT - Default		
lnA	48.9 ± 7.7	
Ea	34.9 ± 5.0	kcal/mol
R^2	0.993	
Q^2	0.961	

Risk based Shelf–Life prediction

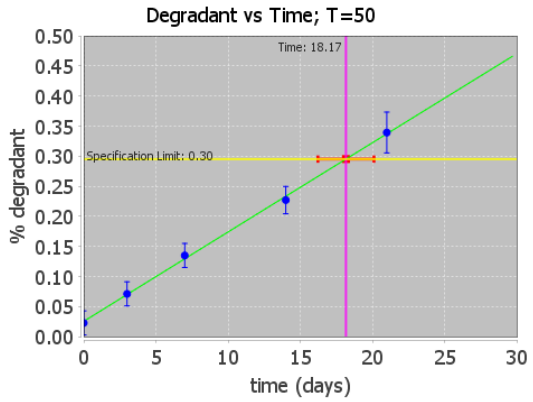
- 2nd degradant → Avromi *vs* Default modelling

Potential Specification Limit		AVROMI			DEFAULT	
		0.2 %	1.0%		0.2%	0.3%
5°C	Shelf Life (years)	>3	>3		>3	>3
	Confidence for 2y	96.35%	98.9%		100%	100%
25°C/60%RH	Shelf Life (years)	1.3	2.95		>3	>3
	Confidence for 2y	25.6%	71.4%		98.9%	99.7%
30°C/75%RH	Shelf Life (years)	0.7	1.6		>3	>3
	Confidence for 2y	2.7%	35.9%		89.3%	96.8
40°C/75%RH	Shelf Life (years)	0.2	0.5		0.7	1
	Confidence for **6 M**	0.68%	57.9%		79.4	96.6

→ Cross-validation with long term data needed

Risk based Shelf–Life prediction

- Degradation kinetics are interconnected
  - Control primary degradation → control 2nd degradation
- More realistic SL prediction → sum of main degradants
- Linear fit



FIT – First order		
lnA	42.0 ± 6.1	
Ea	29.7 ± 3.9	kcal/mol
R^2	0.996	
Q^2	0.986	

Risk based Shelf–Life prediction

- Based on “sum of main degradants”

Potential Specification Limit for sum			0.2 %	0.6%	1.1%
5°C	Glass bottle	Shelf Life (years)	>3	>3	>3
		Confidence for 2y	99.9%	100%	100%
25°C/60%RH	Glass bottle	Shelf Life (years)	1.8	>3	>3
		Confidence for 2y	42.9%	96.4%	99.7%
30°C/75%RH	Glass bottle	Shelf Life (years)	0.8	2.5	>3
		Confidence for 2y	2.5	67.3%	96.1%
40°C/75%RH	Glass bottle	Shelf Life (years)	0.2	0.5	1.0
		Confidence for **6 months**	0	57.5%	99.2%

→ Suspension is stable for 2 years at 25°C/60%RH

→ Climatic zone III/IV will depend on spec setting

Conclusions

- 2nd degradation reactions; modelling of individual components may not be representative

  → Sum of main degradants for SL prediction

- Cold storage is acceptable up to 2 years for the suspension
- RT storage can be considered (climatic zone I/II)
- RT storage Climatic zone III/IV depends on spec setting

  → Validation with long term data needed

Reconstituted oral suspension is currently selected for development as final commercial formulation

Thank you for listening!

Special thanks to:

Bo Li – Hana Prokopcova - Maarten Vliegen – Riet Dams – Steffanie Verhaert

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