



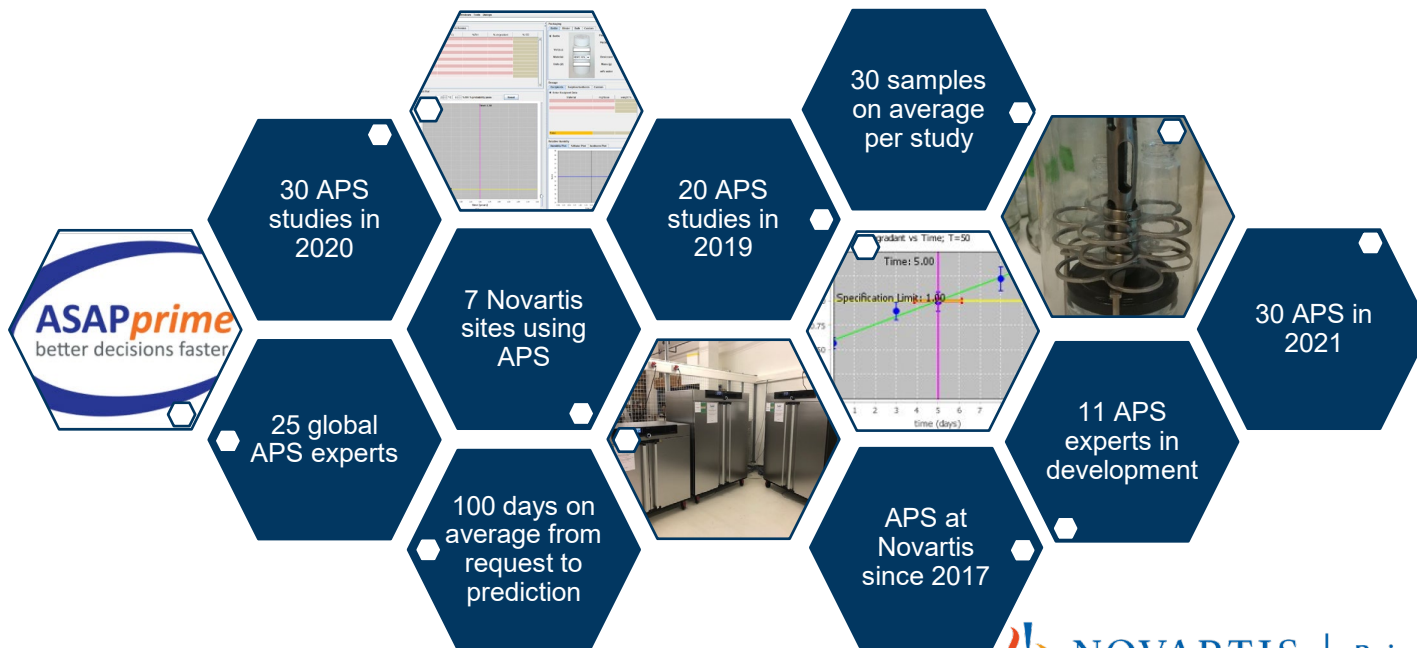
Technical Research and
Development

Comparison of APS data with real time data

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Science of Stability, Philadelphia
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APS at Novartis

- Accelerated Predictive Stability overview

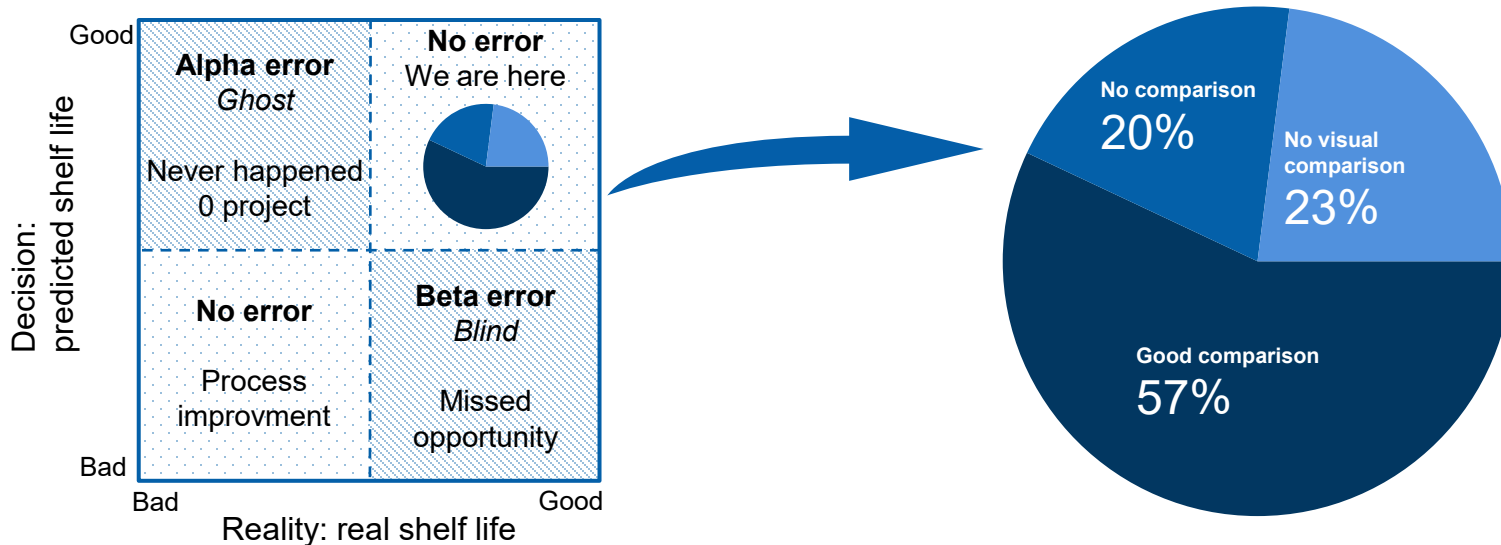


Summary of APS projects

- Summary of 18 APS studies done on Drug Substance or Drug Product

Projects	APS Studies		ICH Studies		
	Shelf-life (years)	Storage condition (°C/%RH)	Shelf-life (months)	Storage condition (°C/%RH)	Packaging
1	> 3	5	18	2-8	HDPE 175/30, 2g Silica
2	> 3	25/60	24	2-8	HDPE 175/30
3	> 3	25/60	24	25/60	HDPE 175/30, 2g Silica
4	> 3	25/60	24	2-8	HDPE 90/30 / ALU blister
5	> 3	5	18	2-8	HDPE 175/30
6	> 3	5	36	2-8	Amber glass vial
7	> 3	5	36	2-8	Glass vial
8	> 3	25/60	24	25/60	HDPE 175/30
9	> 2	25/60	24	25/60	HDPE 175/30
10	> 3	5	21	2-8	HDPE 175/30, 1g Silica
11 to 13	No impurities data to compare (stable)				
14 to 18	Project stopped				

APS overview on shelf life



- All APS projects match well with predicted shelf life and real shelf life
- No alpha error (no over-predicting the shelf life) and beta error (missing opportunity by under-estimating the shelf life)

Focus on 2 examples

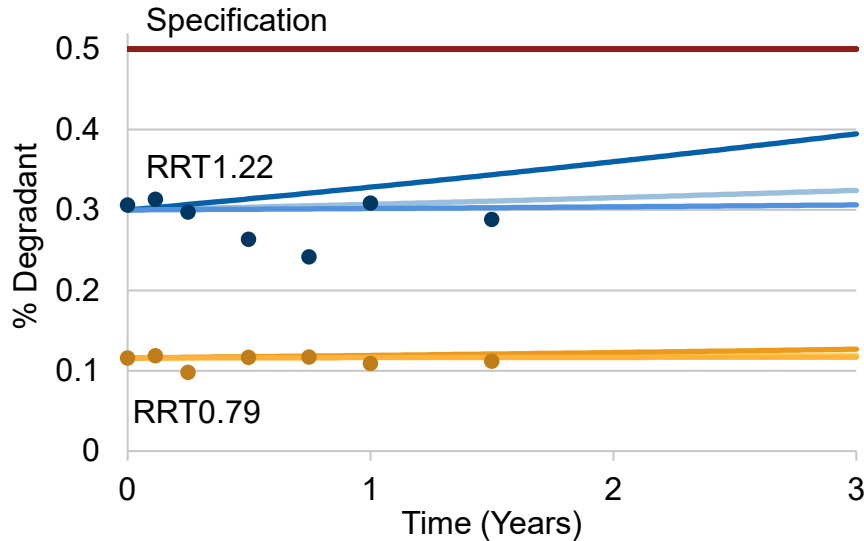
- Focus on 2 examples for oral and parenteral drug products with comparison of prediction vs real time data

Projects	APS Studies		ICH Studies		
	Shelf-life (years)	Storage condition (°C/%RH)	Shelf-life (months)	Storage condition (°C/%RH)	Packaging
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APS N°3



DP Hard capsule: comparison of data on 2 major impurities at 25°C/60%RH

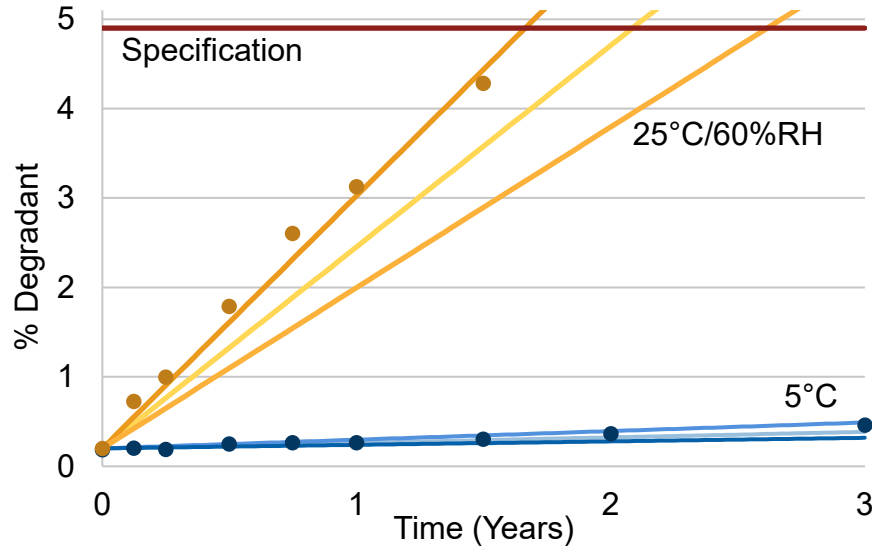


Major impurities	RRT1.22	RRT0.79
Arrhenius Equation: $\ln k = \ln A - Ea/(RT) + B(RH)$	$\ln k = 40.28 - 31.64 / (60.25)$	$\ln k = 21.96 - 19.52 / (60.25)$
B	0.013	0.018
R ²	0.708	0.983
MAPD by ASAPprime®	8%	4%
Slope comparison factor by Novartis	-105%	-61%

- Slight discrepancy observed between the 2 comparisons' method
- Higher value for the slope comparison due to variability in real time data

APS N°7

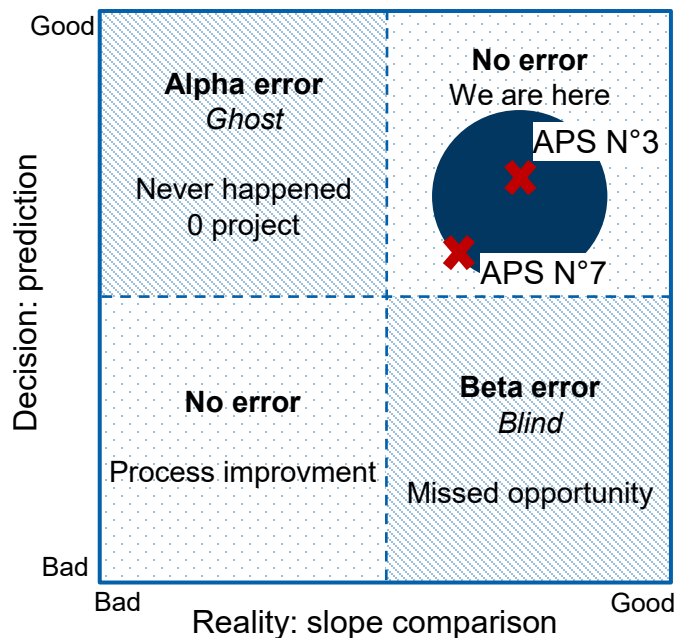
DP liquid in vial: comparison of data for 1 impurity RRT 0.76 at 2 conditions



Major impurities	RRT 0.76	
Arrhenius Equation:	$\ln k = \ln A - \frac{Ea}{RT}$	$\ln k = 45.03 - 29.67 / (60.5)$
R^2	1.000	
Q^2	0.999	
MAPD by ASAPprime®	21% at 25°C	10% at 5°C
Slope comparison factor by Novartis	13% at 25°C	50% at 5°C

- The 2 comparisons' method are more aligned for this example
- Most likely due to less variability in real time data

Conclusion



- Novartis uses APS in development and is expanding to commercial
- Full slope comparison using the 2 methods for all APS studies on going
 - Acceptable range still to be defined when more comparison available
 - Selection of the method still to be done
- No alpha error (no over-predicting the shelf life) and beta error (missing opportunity by under-estimating the shelf life)

Excellent fit between prediction and reality



Thank you