ACCURATE PREDICTION OF THE CHEMICAL STABILITY OF THE PANCURONIUM AND ITS DEGRADATION PRODUCTS IN INJECTABLE SOLUTION

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CONTEXT AND OBJECTIVE

- ☞ Development of a Pancuronium 2 mg/mL injectable formulation
- ☞ Stability study requirement was performed by classical ICH and non classical semi-predictive methodology

Objective : to compare the prediction of the chemical stability of the drug by Accelerated Stability Program (ASP) with the results of a classical ICH method

METHODS

Stability studies design

APS methodology (non classical)

Storage conditions	Times of analysis
5 ± 3 °C (long term storage)	D0 ; D15 ; D30 ; D365
25 ± 2 °C 60% RH ± 5% RH 40 ± 2 °C 75% RH ± 5% RH 60 ± 2 °C (accelerated storages)	D0; D15; D30; D45; D60; D90

ICH methodology (classical)

Storage conditions	Times of analysis
5 ± 3 °C (long term storage)	D0 ; D30 ; D180 ; D365

Non linear modeling was performed with « R » studio
Best fitted model was selected with AIC ; BIC and RMSE
Extrapolation was performed over 2 years

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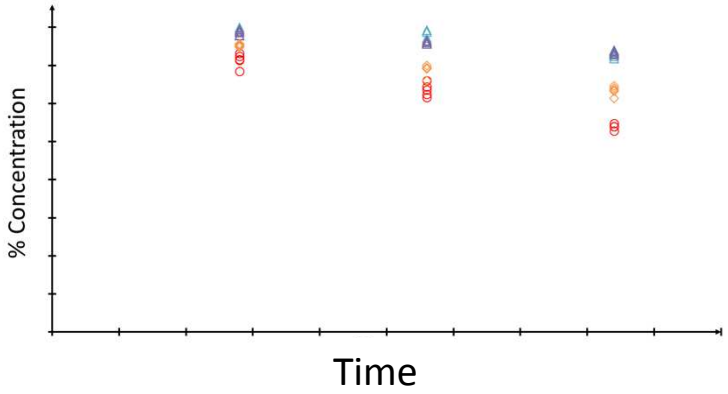
METHODS

APS methodology : principles

1) Force the degradation of a drug over a short period of time



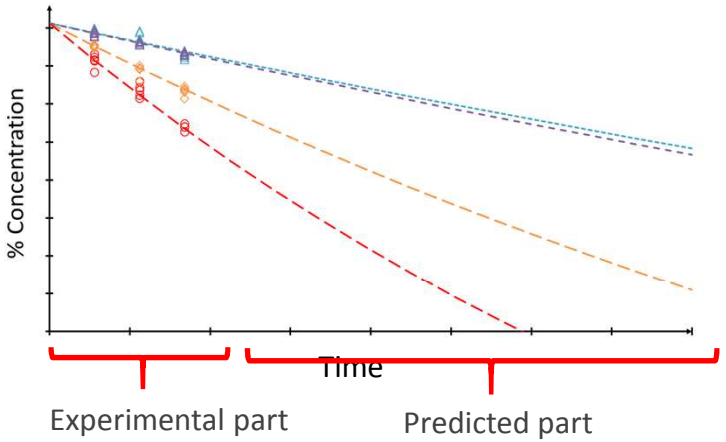
○ 40 °C / 75 % HR
□ 30 °C / 65 % HR
△ 25 °C / 60 % HR

2) Best fitted model screening

Tableau 7 : synthèse des équations d'avancement de réaction selon les modèles cinétiques en phase homogène et hétérogène.

Phase	Modèle cinétique	Equation d'avancement de la réaction α(t) =	
		Modèles de réaction basés sur les ordres	
Cinétique en phase homogène	Ordre 0	$kt.[H]^N$	$kt.\exp(N.H)$
	Ordre 1	$(1-e^{-kt}).[H]^N$	$(1-e^{-kt}).\exp(N.H)$
	Ordre 2	$\left(1-\frac{1}{1+kt}\right).[H]^N$	$\left(1-\frac{1}{1+kt}\right).\exp(N.H)$
	Ordre 3	$(1-(1+kt)^{-0.5}).[H]^N$	$(1-(1+kt)^{-0.5}).\exp(N.H)$
		Modèles de réaction basés sur les ordres	
Cinétique en phase hétérogène	Ordre 0	$kt.[H]^N$	$kt.\exp(N.H)$
	Ordre 1	$(1-e^{-kt}).[H]^N$	$(1-e^{-kt}).\exp(N.H)$
	Ordre 2	$\left(1-\frac{1}{1+kt}\right).[H]^N$	$\left(1-\frac{1}{1+kt}\right).\exp(N.H)$
	Ordre 3	$(1-(1+kt)^{-0.5}).[H]^N$	$(1-(1+kt)^{-0.5}).\exp(N.H)$
		Modèles de réaction de type nucléation	
	Réaction en puissance (d'ordre « n »)	$((kt)^n).[H]^N$	$((kt)^n).\exp(N.H)$
	Nucléation (JMAEK)	$(1-e^{-(kt)^n}).[H]^N$	$(1-e^{-(kt)^n}).\exp(N.H)$
	Auto-catalyse (Prout-Tompkins)	$((1+(e^{kt})^{-1})^{-1}).[H]^N$	$((1+(e^{kt})^{-1})^{-1}).\exp(N.H)$
		Modèles de réaction de type diffusion	
	Diffusion sur 1 dimension	$((kt)^{1/2}).[H]^N$	$((kt)^{1/2}).\exp(N.H)$
	Diffusion sur 3 dimensions (Jander)	$(1-\left[1-(kt)^{\frac{1}{3}}\right]^n).[H]^N$	$(1-\left[1-(kt)^{\frac{1}{3}}\right]^n).\exp(N.H)$
		Modèles de réaction de type contraction	
	Contraction de surface (n = 2) ou contraction de volume (n = 3)	$(1-(1-kt)^n).[H]^N$	$(1-(1-kt)^n).\exp(N.H)$

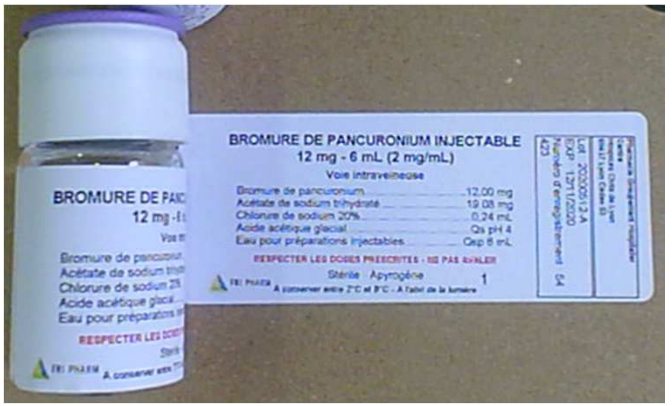
3) Extrapolate



METHODS

Production of 1 batch of Pancuronium 2 mg/mL

Qualitative and quantitative composition	
Pancuronium dibromide	12 mg
Sodium acetate trihydrate	19.08 mg
Sodium chlorure 20 %	0.24 mL
Water for injection	Qsp 6 mL
Colorless type I glass	1
Bromobutyl rubber stopper	1



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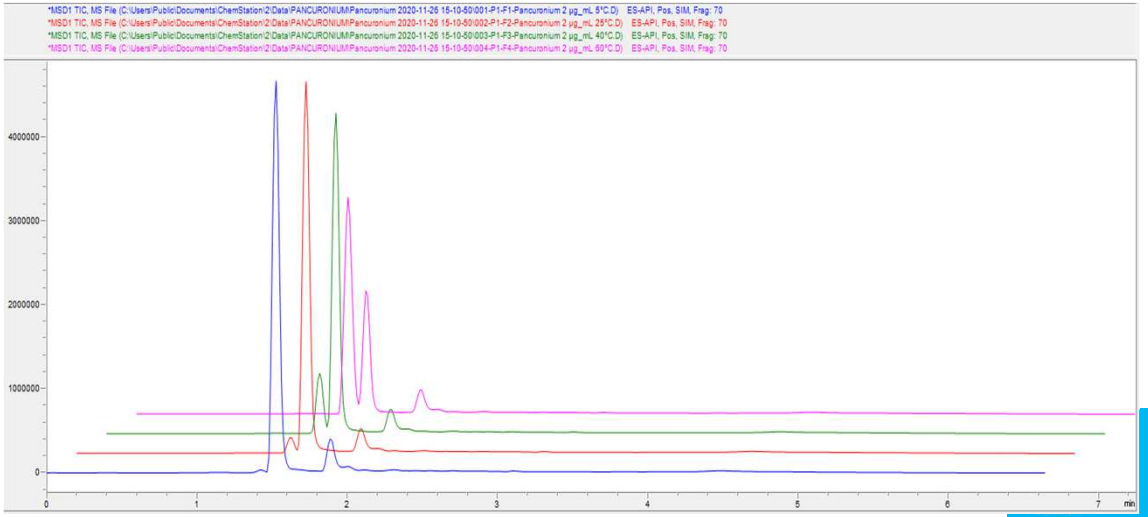
METHODS

Quantification of pancuronium and its degradation products by ultra-high performance liquid chromatography tandem with mass spectrometry (UHPLC-MS)

	UHPLC Parameters
Stationary phase	Kinetex® C_{18} ; 100x2.1 mm ; 2.6 µm ; 30 °C
Mobile phases	Phase A : ammonium formiate 5 mM pH = 3 Phase B : acetonitrile + 10 % phase A Gradient of Phase A : Phase B 0-2 minutes : from 90 : 10 to 10 : 90 2-3 minutes : 10 : 90 3-4 minutes : from 10:90 to 90 : 10 4-5 minutes : 90 : 10 Flow = 0.5 mL/min
Injection	2 µL

	MS Parameters
ESI Source	Capilary voltage = 3 000 V Gaz flow : 12 L/min Gaz temperature : 350 °C



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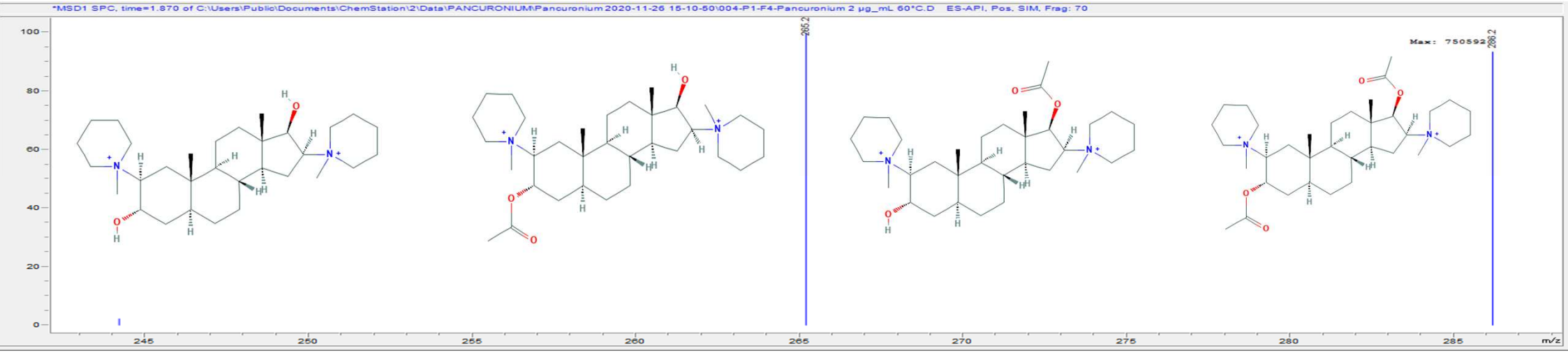
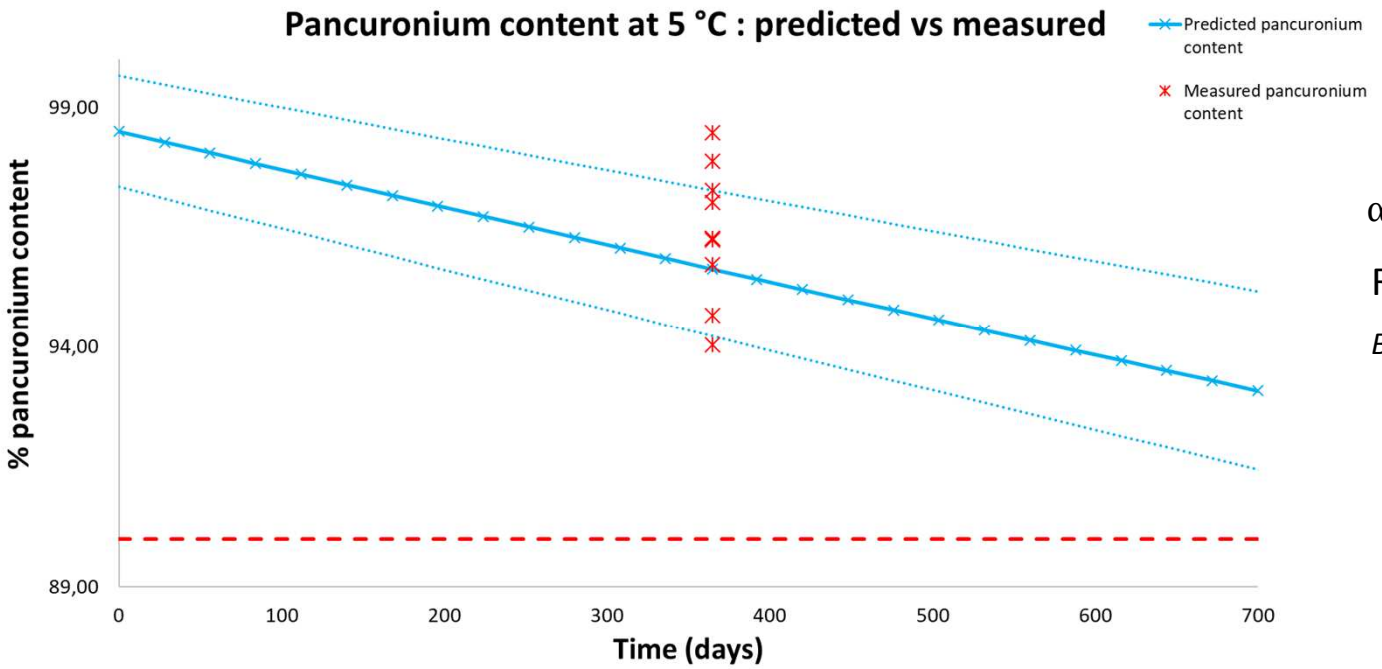
RESULTS : MS SPECTRAS → 4 MOLECULES



244.2 m/z | 265.2 m/z | 286.2 m/z

Compounds	Ret time (min)	Ratio m/z
Pancuronium	1.40	286.2
Dacuronium (impurity A Ph.Eur) and / or 3-desacetylpancuronium (impurity B Ph.Eur)	1.35 1.45	265.2
3,17-didesacetylpancuronium (impurity C)	1.15	244.2

M12 PREDICTED VS MEASURED PANCURONIUM CONTENT



$$\alpha(t) = \alpha(0) + K3.(1 - \exp(-K1.\exp\left(\frac{-K2}{T}\right)))$$

Reaction order > 0

BIC = -237,4 ; AIC = -248,1 ; RMSE = 3,98

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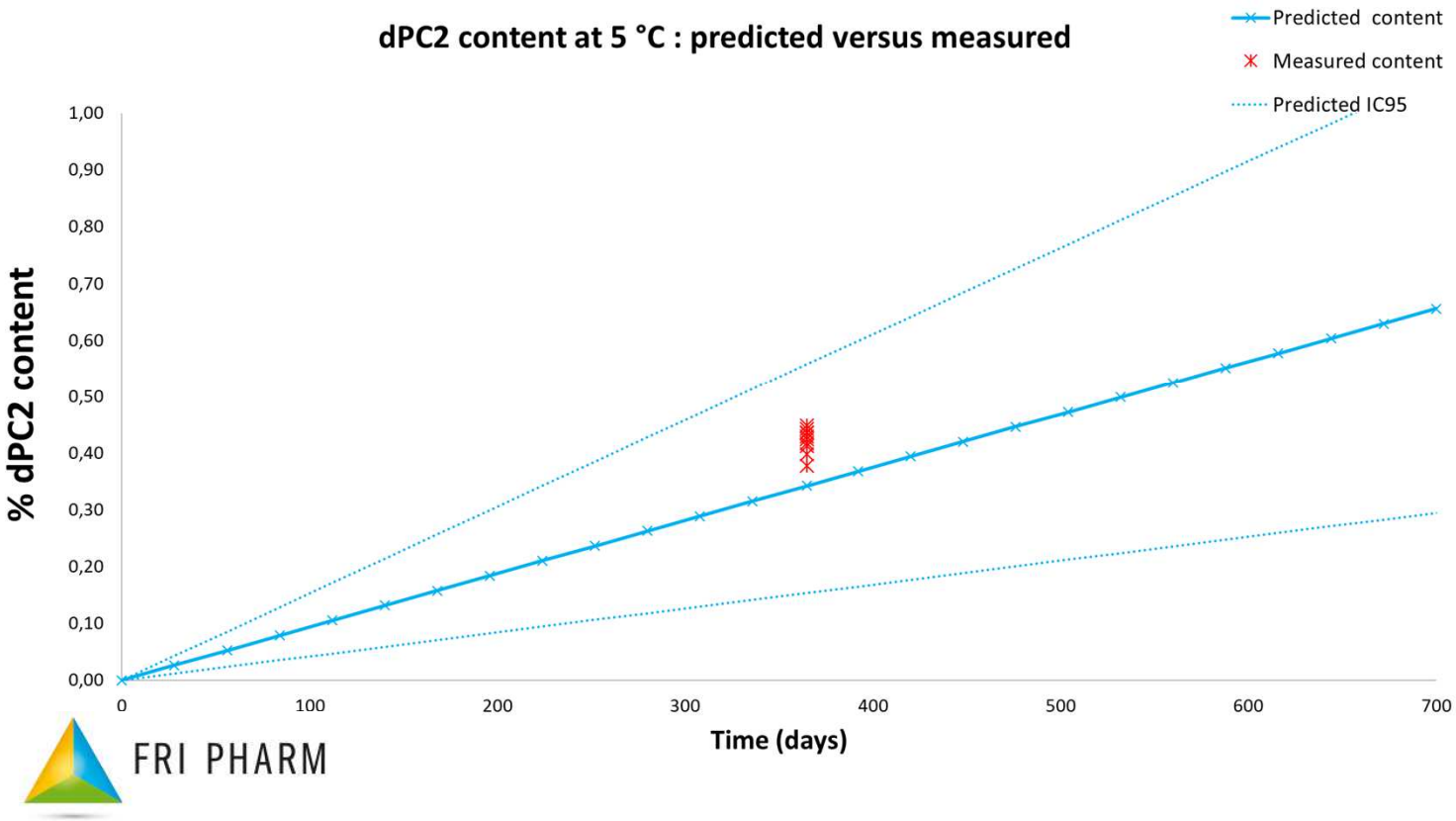
M12 PREDICTED VS MEASURED IMPURITY A (PH.EUR)



Zero order like model

BIC = 232,9; AIC = 220,0 ; RMSE = 0,96

Specification : NMT 1.0 % (Ph.Eur)

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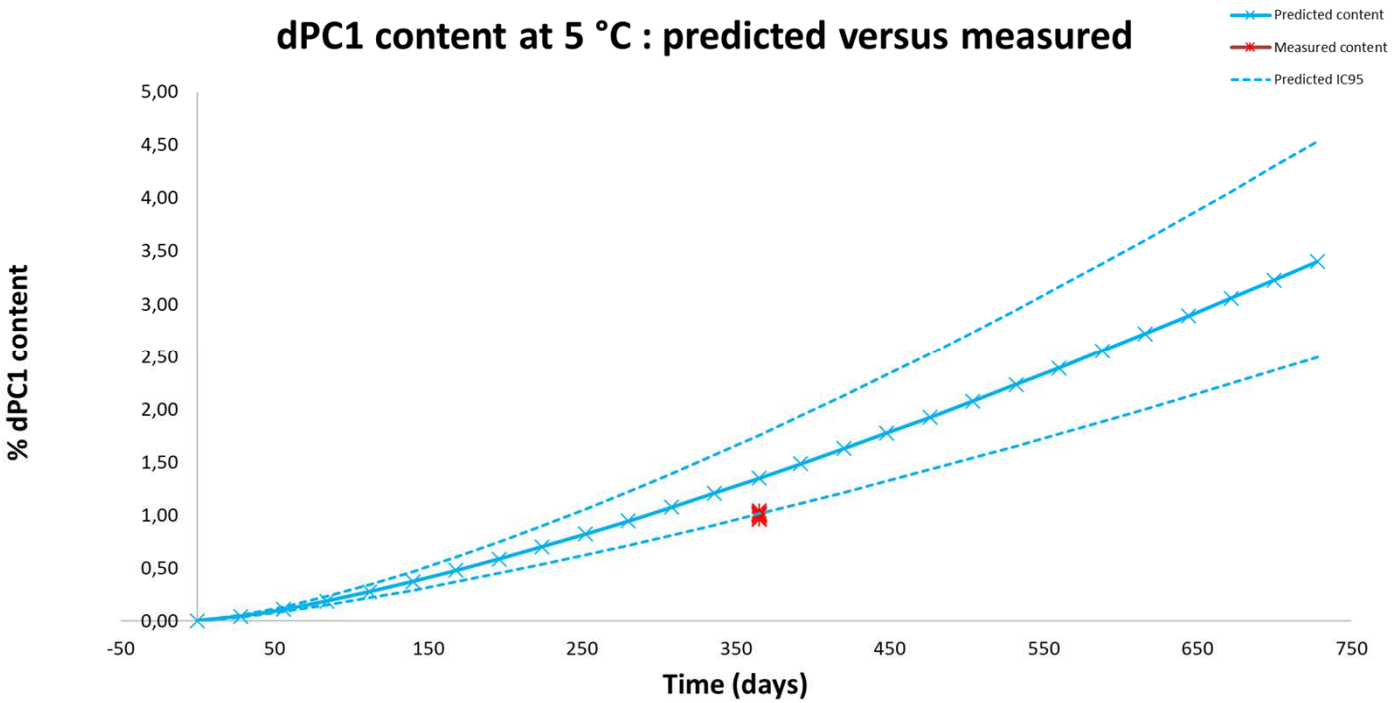
M12 PREDICTED VS MEASURED IMPURITY B PH.EUR



Autocatalytic model (Prout-Tompkins)

BIC = 213,3 ; AIC = 202,4 ; RMSE = 0,82

Specification : NMT 3.0 % (USP)

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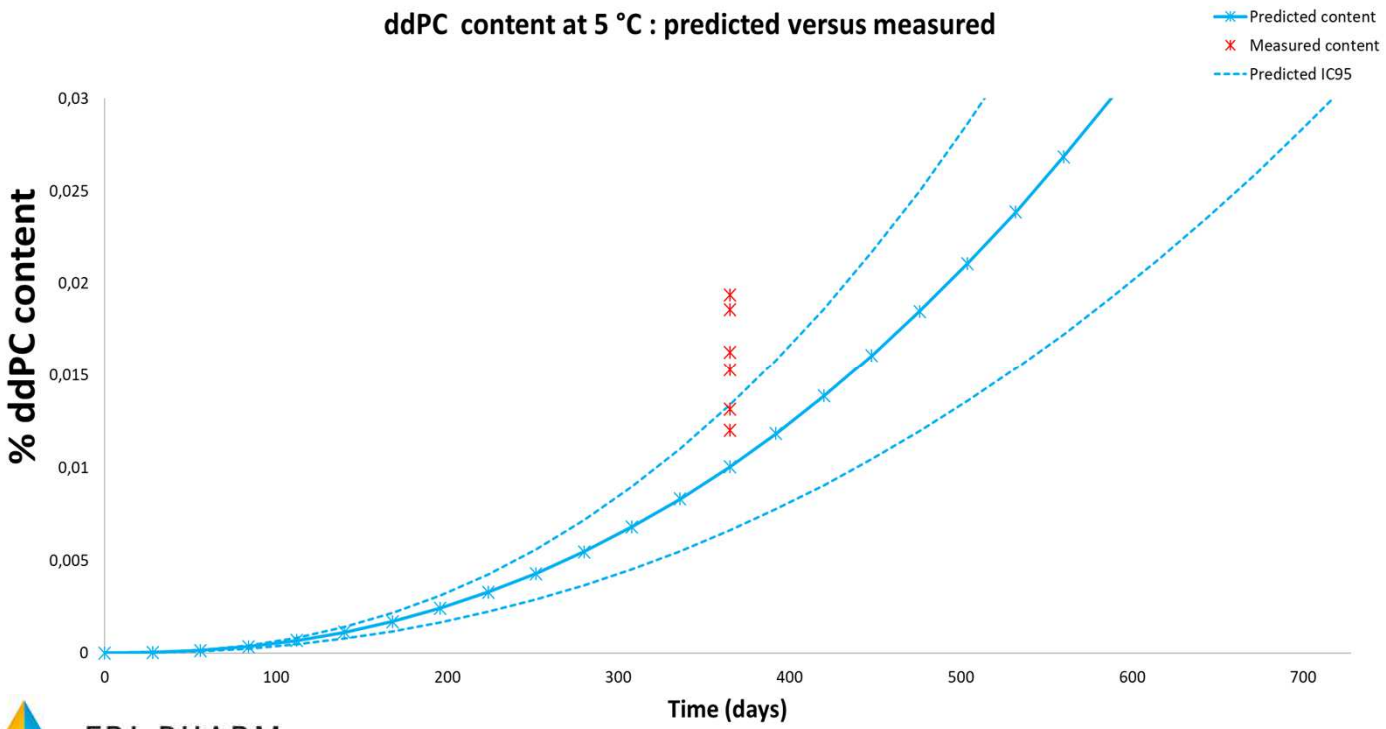
M12 PREDICTED VS MEASURED IMPURITY C USP



Nucleation like model

BIC = 131,5 ; AIC = 120,6 ; RMSE = 0,56

Specification : NMT 2.0 % (USP)

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DISCUSSION

☞ Good correlation between predicted and measured content for Pancuronium and its degradation products at D365

☞ A shelf life of 2 years can be predicted, thus the specification limit will be met for impurity B

☞ Confirmation will be done at D720

☞ Stability prediction with APS method can be a relevant tool for many application, e.g., drug development, shelf life prediction, API salt selection, temperature excursion management.

THANK YOU

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