Procaine : a correlation study between predicted and observed stability & application to the estimation of a preliminary expiry date

TOUSSAINT Balthazar[a,b], LEGRAND Pauline[a,c], RIBIER Zoé[a], BOCCADIFUOCO Gaëtan[a], WOJCICKI Amélie[a], BOUDY Vincent[a], GOULAY-DUFAY Sophie[a]

[a] *Laboratoire de Développement Analytique, Agence Générale des Equipements et Produits de Santé, AP-HP, Paris, France*
[b] *Institut Galien Paris-Sud, CNRS, UMR 8612, LabEx LERMIT, Université Paris-Saclay, Faculté de Pharmacie, 5 Rue J.-B. Clément, Châtenay-Malabry, France*
[c] *Unité de Technologies Chimiques et Biologiques pour la Santé, UMR8258 Inserm U1022, Université Paris Descartes, Faculté de Pharmacie, 4, av de l'Observatoire, Paris, France*

A liquid form of procaine is manufactured by Paris Hospital Public Pharmaceutical Establishment for cardioplegia in cardiac surgery. Procaine is mainly degraded by hydrolysis in para-aminobenzoic acid (PABA) and necessitates refrigerated storage conditions. However the process and clinical practices expose the drug to high temperature. The aim our study was to evaluate in a prospective maner the time of each step in order to control the amount of PABA produced and guarantee that is still under the limit set with regards to toxicological evaluation.

Materials & Methods

Arrhenius modelization

Samples were prepared with a concentration of 13.6 mg/mL of procaine and then exposed to high temperature to mimic moist heat sterilization method.

They were stored at different temperatures : 5°C (n=9), 25°C (n=21), 30°C (n=6), 40°C (n=8). The proportion of measured PABA (m/m %) was divided by the time of exposure to obtain a kinetic constant (%PABA/month). A mathematical model was modeled to calculate the PABA content for long storage conditions.

"Real life" data

One batch has been produced and studied at 5°C and 25°C. A linear regression was performed on PABA content.

Analysis system and sample preparation

All analysis were performed by HPLC-PDA system, which permitted to measure concentrations of procaine et PABA. The results used in this study are the mass ratio between PABA and procaine (% m/m).

Comparison between predicted and real life data

On initial content of PABA, %PABA/month, and time needed to observe 1.0% of PABA (toxicological limit approved at expiration date).

The most restrictive kinetics & initial content of PABA have been used for the evaluations of the impacts of temperatures on long term stability, in order to have a first preliminary expiry date.

Results

1) The **kinetics** of the hydrolysis reaction is **constant** in time, reaction of **order 0 :**

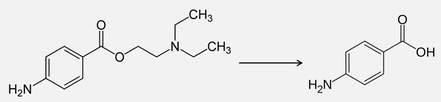

Fig. 1 : Hydrolysis of procaine into PABA

2) The **mean initial content of PABA** due to the sterilization process is **0.81%**, with a coefficient of variation of 9.8%.

Real life data shows an initial content of **0.75% of PABA**.

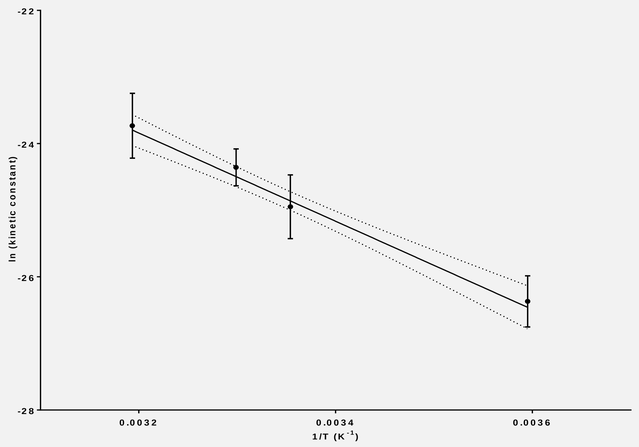

Fig. 2 : Arrhenius modeling on PABA apparition kinetic

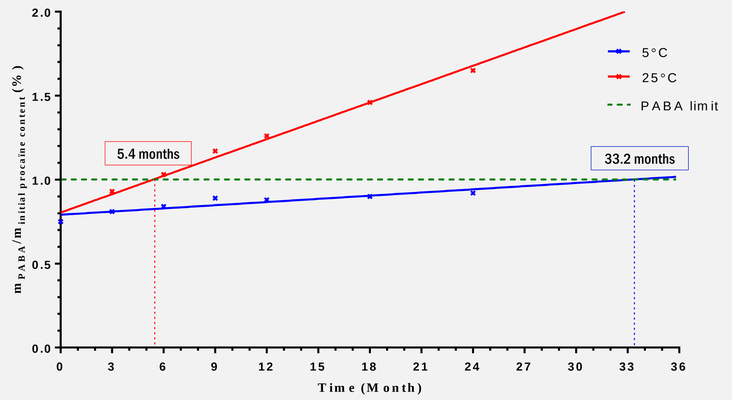

Fig. 3 : Evolution of PABA during stability study

3) Results of **predicted and real life data** are resumed into the table :

Parameter	5°C		25°C	
	Predicted	Observed	Predicted	Observed
%PABA/Month	0.0086	0.0088	0.0423	0.0397
Time needed to reach 1.0% (months)	29.2	33.2	5.9	5.4

Application to real life scenario

The predictive model based on Arrhenius equation matches with real data found on one batch . It can therefore be applied to evaluate the impact of temperature over 5±3°C during process and clinical practices. The actual process needs 8 days at 25°C. If needed for clinical practices, the product can be exposed no more than 3 days to 25°C. In total If the drug is exposed to 11 days. The expiration date was then evaluated to make sure that PABA amount stays under 1.0% at expiration date.

$$Maximal\ intake = PABA\ limit - Amount(Sterilization) - Amount(25°C) = 1.00 - 0.81 - 0.01 = 0.18$$

$$Maximum\ preliminary\ expiry\ date = \frac{maximal\ intake}{Arrhenius\ kinetic\ constant\ at\ 5°C} = \textbf{21 months at 5°C}$$

Conclusions

1) The **predictive model** based on Arrhenius equation **match** with real data found on one batch
2) **Specification limit** of PABA at release was set at **0.8%** (m/m) according to the data on production process.
3) An **18 month expiration** date under **refrigerated conditions** was fixed
4) A **3 days exposure to 25°C for hospital practices needs was permitted without impact on long term specification limit** of 1% m/m of PABA. However, **after exposure** to 25°C the product should be **immediately thrown away**.
5) All these **limits will be challenged** with the production of other batches.