

**Mailing address:**

P.M. Tulkens  
av. Mounier 73 (B1.73.05)  
1200 Brussels, Belgium.  
tulkens@facm.ucl.ac.be

# Variations in dissolution time, coloring, and stability in concentrated solutions of original and generics of meropenem

Isabelle K. Delattre, Françoise Van Bambeke & Paul M. Tulkens

Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

## Background

Economic pressures and legal constraints increasingly force hospital pharmacies to purchase generic drugs rather than original branded products but originals themselves may also be offered at competing prices. For instance, in Belgium in 2017, the original and two generics of meropenem are proposed to hospitals at a price about half that of the original in 2011.

Yet, differences in key properties have been noted between suppliers of meropenem even though the preparations proposed to the hospitals are approved by local health authorities.

This has raised concerns among clinicians about drug quality when dealing with patients in critical conditions such as in Intensive Care Units where ease of preparation, efficacy, and stability of the prescribed antibiotics are of paramount importance.

In the context of an EU-sponsored program aiming at monitoring the serum levels of meropenem and other  $\beta$ -lactams in critically-ill patient, we have compared meropenem samples obtained from selected suppliers in Belgium, France and Spain.

## Methods

We compared one original of meropenem (MERONEM®; AstraZeneca) and generics from approved suppliers at the time of purchase (Sandoz, Hospira, Fresenius-Kabi [both Belgium and France], and Aurovit).

All products were obtained as dry powders (to be reconstituted for parenteral administration) from hospital pharmacies and used as directed by the corresponding supplier.

We tested for:

1. the rate of dissolution (by experienced nurses) of the preparations upon addition of the recommended solvent, using both visual examination and nephelometric measurement;
2. the coloring of the reconstituted concentrated solutions upon storage at fixed temperatures for up to 8h, using spectrophotometric quantitative analysis;
3. the rate of disappearance of meropenem upon analysis of the reconstituted solutions using a validated LC-MS-MS method (detection and quantification of meropenem as molecular ion with mass/charge ratio of 384/141.32, with deuterated meropenem as internal standard). Decay data were analyzed by linear regression with initial point (0 h) set at 100% and calculation of the 95% confidence interval and standard deviation [Prism 7.02]).

## Conclusions

- Substantial differences in dissolution, release of degradation products and loss of drug are served between the original of meropenem and its generics, and between generics.
- Our observations call for
  - attention in the selection of a suitable supplier to avoid administration of lower than expected doses (loss of efficacy) and exposure to undissolved and/or degradation products (risk of toxicity);
  - more stringent quality controls for generics compared to original products by Public Health Authorities.

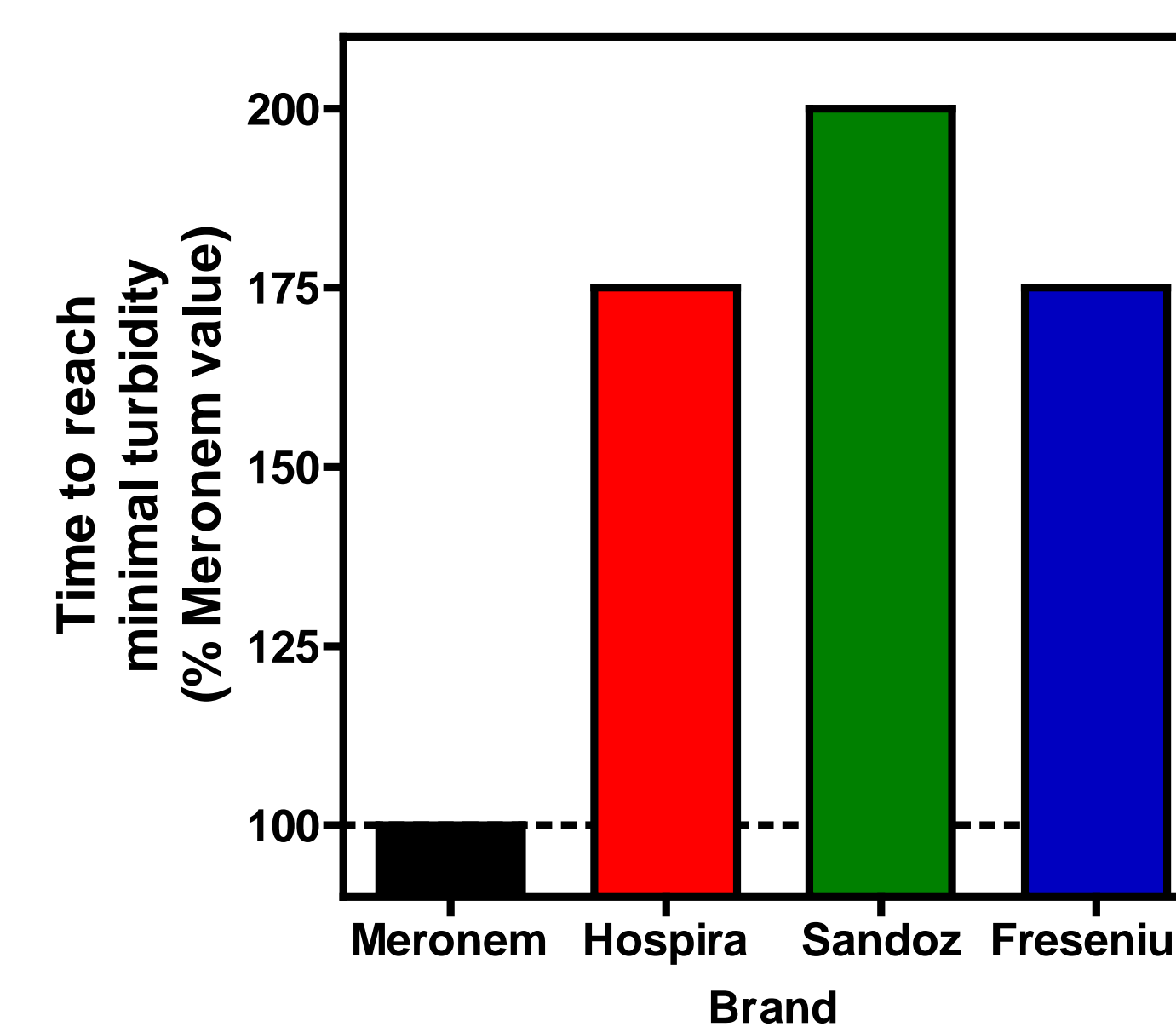
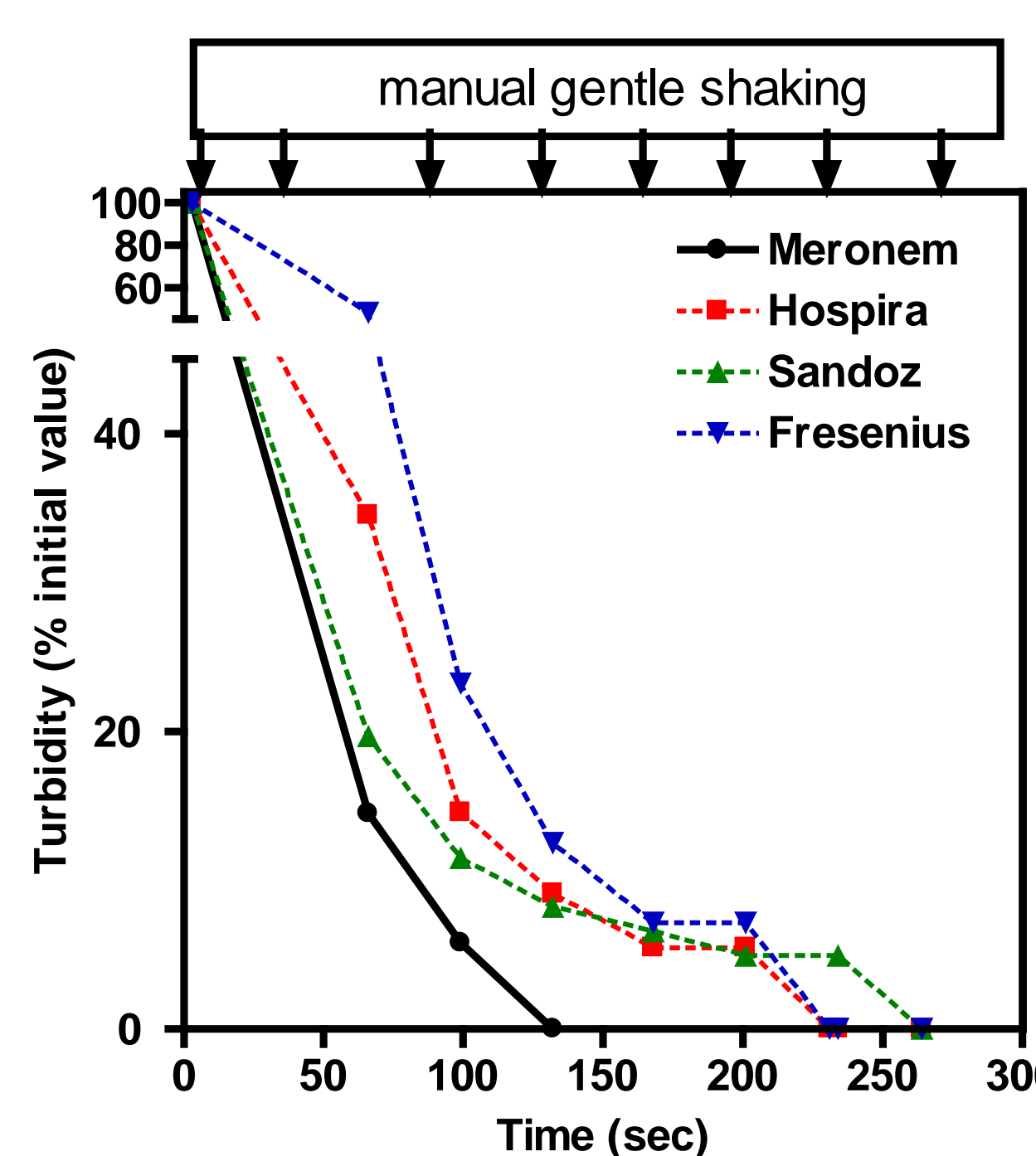
## Acknowledgments

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## Results

### 1. Rates of dissolution (experienced nurses)

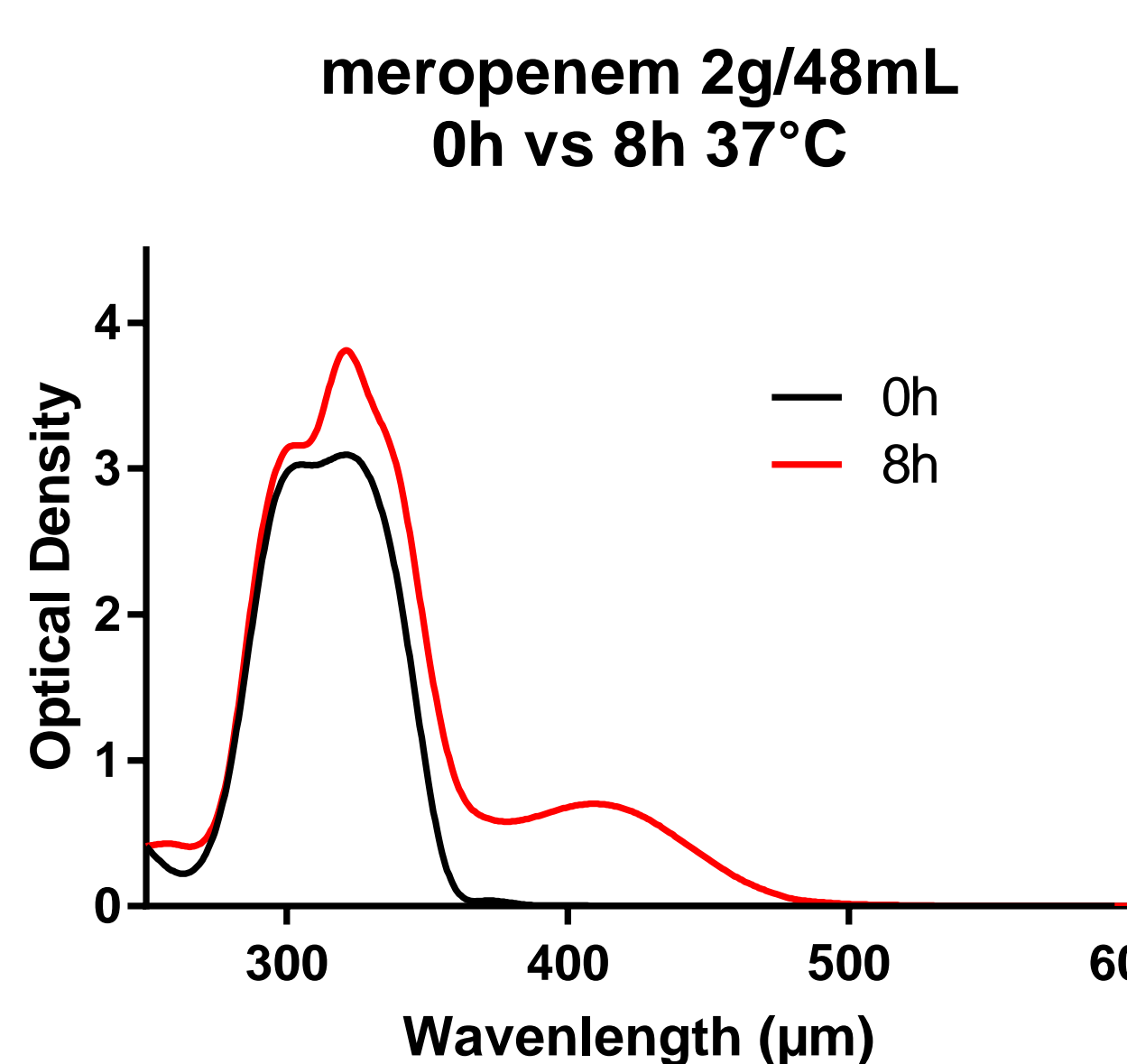
- Drug concentration: 50 mg/mL (as used for bolus administration)
- gentle manual shaking followed by turbidity measures (Mc Farland);
- room temperature



→ compared to the original (MERONEM®) all 3 generics require about twice longer a time to achieve complete dissolution

### 2. Coloring (appearance of degradation products)

- Drug concentration: 1 and 2 g/48 mL (as used for extended infusion)
- full spectrophotometric scan (change in absorption spectrum);
- increase in OD



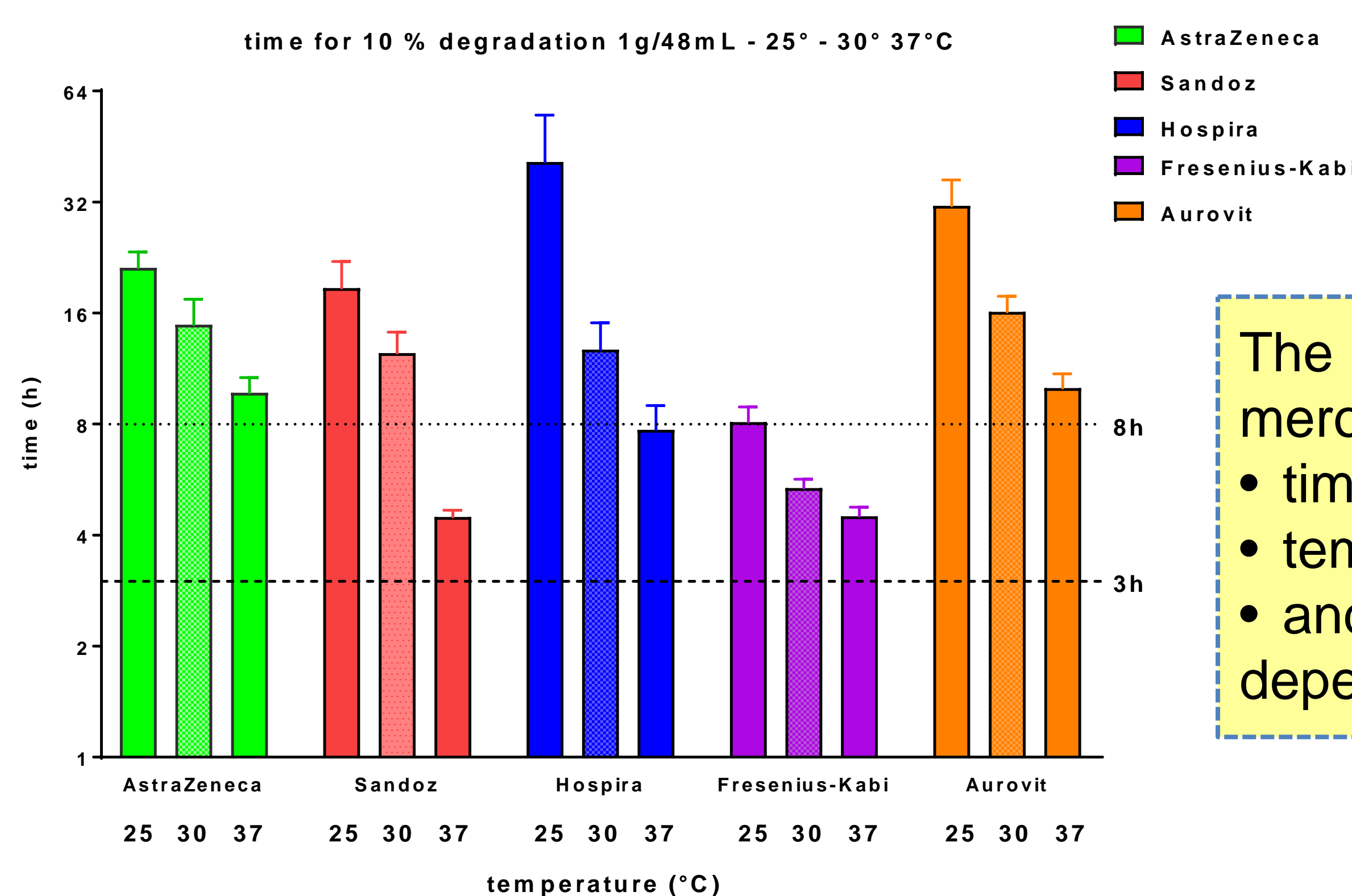
Absorbance<sub>405nm</sub> of Degradation Products after 8h \*

Brand	1g/48mL			2g/48mL		
	25°C	30°C	37°C	25°C	30°C	37°C
AstraZeneca	0.680	0.735	0.873	0.978	1.013	1.198
Sandoz	0.936	1.034	1.212	1.741	1.924	2.207
Hospira	0.705	0.766	0.797	1.039	1.083	1.266
Fresenius-Kabi (BE)	0.701	0.789	0.847	1.115	1.166	1.537
Kabi (FR)	0.566	0.586	0.729	0.861	0.963	1.137
Aurovit	0.723	0.775	0.798	1.100	1.186	1.368

\* After subtraction of meropenem OD

→ degradation products are generated from all sources of meropenem. Some sources (SANDOZ, e.g.) produce considerably more...

### 3. Loss of meropenem (time needed to loose 10% [EU pharmacopoeia])



The loss of meropenem was

- time-
- temperature-
- and concentration-dependent

→ while the original and 2 generics are stable for up to 8h at 37°C, other generics (Sandoz, Fresenius-Kabi) are not ...