Assessing the stability of piperacillin/tazobactam at 25 mg/mL and 90 mg/mL reconstituted and diluted in 0.3% w/v citrate buffered saline in two commercially available elastomeric devices.

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INTRODUCTION

The stability of antimicrobial agents is an important consideration for outpatient parenteral antimicrobial therapy (OPAT) services, particularly when using ambulatory devices for continuous infusion over an extended “in-use” time.

Piperacillin/tazobactam (Pip/Taz) is a broad-spectrum penicillin/beta-lactamase inhibitor combination antibiotic with activity against a wide range of pathogens including multi-drug-resistant Gram-negative organisms such as *Pseudomonas aeruginosa*. Optimal administration of piperacillin/tazobactam is at 6-8 hourly intervals, which is unfeasible for OPAT services.

We have assessed the stability of piperacillin/tazobactam via continuous 24-hour infusion in two different commercially available elastomeric devices: (1) FolFusor LV10 (Baxter Healthcare) and (2) Easypump II (B.Braun), in accordance with NHS Yellow Cover Document (YCD) standards[1]. A published study extended stability of flucloxacillin when the drug was reconstituted and diluted using 0.3% w/v citrate buffered saline in elastomeric devices for OPAT[2]. This same approach was adopted for the present study with piperacillin/tazobactam and supported extended stability.

METHODS

Piperacillin/tazobactam was reconstituted and diluted in 0.3% w/v citrate-buffered saline pH 7.0 at two therapeutic concentrations of the drug combination (25 mg/mL and 90 mg/mL). At each concentration the solution was distributed into the elastomeric pump devices which were assessed for stability under simulated clinical practice conditions. Devices were refrigerated at 2-8°C for 13 days, followed by a 2-3 hours warm up period at room temperature and a 24-hour simulated infusion period at 32°C. Testing was carried out using triplicate devices for the elastomeric pumps. Laboratory testing included subvisible particle counts, pH and visual appearance testing and HPLC analysis at five timepoints.

RESULTS

Results show piperacillin/tazobactam when reconstituted and diluted in 0.3% w/v citrate-buffered saline pH 7.0 is stable for up to 13 days at 2-8°C plus 24-hours administration at 32°C in both elastomeric devices tested.

Both drug solutions were found to be sufficiently stable to meet the requirements of the YCD stability assessments for small molecules1 (±5% of initial drug concentration) throughout the study period (Figures 1 & 2).

CONCLUSIONS

This study confirms that when piperacillin/tazobactam solution for injection is reconstituted and diluted using 0.3% w/v citrate buffered saline pH 7.0 it is stable for 13 days in a fridge at 2-8°C, plus a 24-hour period at 32°C at concentrations of 25 mg/mL to 90 mg/mL, simulating clinical practice in the OPAT setting. All data is compliant with the standards of the NHS YCD guidance on stability assessments for small molecules[1]. Piperacillin/tazobactam solutions for injection at the concentrations studied have the potential to allow for single infusion over a 24-hour period. This approach supports a once daily OPAT service delivery model.

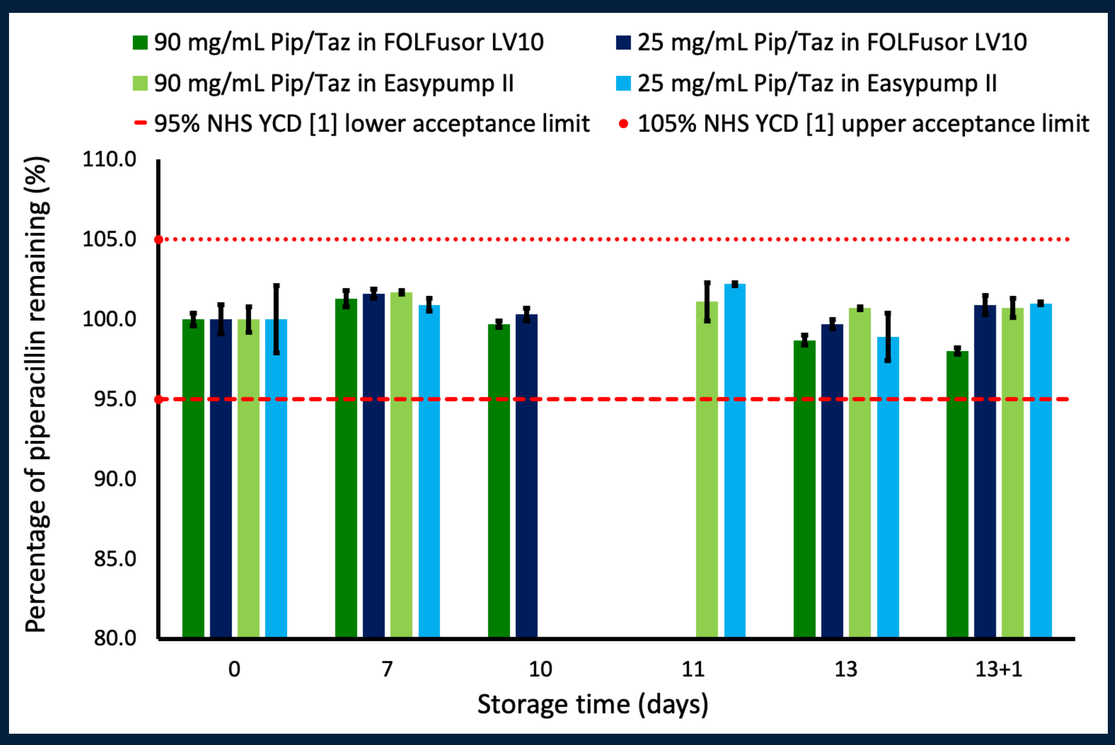

FIGURE 1. HPLC assay of piperacillin in FOLFusor (Baxter) and Easypump®II (B.Braun) devices.

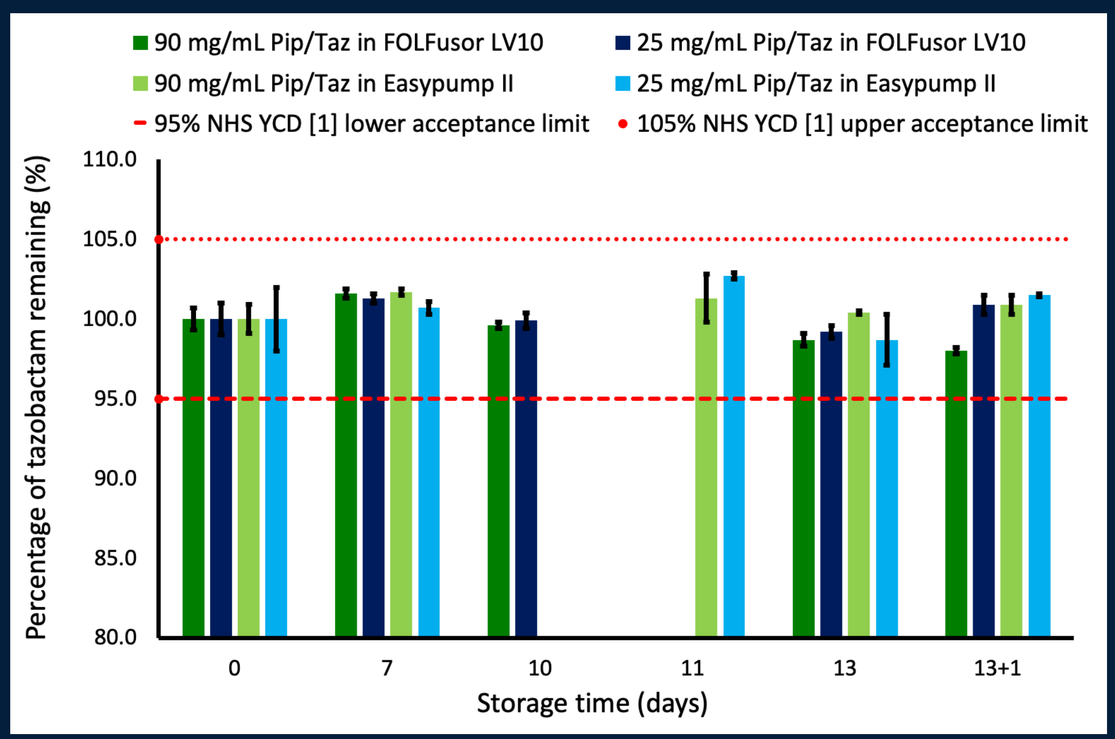

FIGURE 2. HPLC assay of tazobactam in FOLFusor (Baxter) and Easypump®II (B.Braun) devices.

REFERENCES

1) A Standard Protocol for Deriving and Assessment of Stability: Part 1 - Aseptic Preparations (Small molecules) – NHS Pharmaceutical Quality Assurance Committee, Edition 4.
2) Allwood MC, Stonkute D, Wallace A, et al. Assessment of the stability of citrate-buffered flucloxacillin for injection when stored in two commercially available ambulatory elastomeric devices: INfusor LV (Baxter) and Accufuser (Woo Young Medical): a study compliant with the NHS Yellow Cover Document (YCD) requirements. European Journal of Hospital Pharmacy Published Online First: 18 September 2018. doi: 10.1136/ejhpharm-2018-001515.

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