Assessing the stability of ceftolozane/tazobactam (ZERBAXA®) at 5 mg/mL and 20 mg/mL following reconstitution and dilution in 0.9% saline in two commercially available elastomeric devices.

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BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

OPAT Outpatient Parenteral Antimicrobial Therapy

INTRODUCTION

Extended infusions of commercially available antimicrobial agents provide a diversity of treatment options for outpatient parenteral antimicrobial therapy (OPAT) services, especially when the standard dosing for some antimicrobials is 6 or 8-hourly, rendering them impractical for most OPAT services. The use of extended infusions in OPAT requires evidence of the safety and stability of the agent being given by extended infusion, and the NHS Yellow Covered Document[1] outlines the requirements for stability testing. We have previously reported on the stability of flucloxacillin[2] and meropenem[3], piperacillin/tazobactam[4] and ceftazidime[5] as part of the BSAC Drug Stability Testing programme to support OPAT services in the UK and further afield.

Ceftolozane/tazobactam (CLZ/TAZ) is a broad-spectrum cephalosporin/beta-lactamase inhibitor combination with activity against a range of pathogens including expanded spectrum beta-lactamase (ESBL) producing strains of Enterobacteriacae and multi-drug resistant strains of *Pseudomonas aeruginosa*. It is given three times daily, making it unsuitable for OPAT services at this dose frequency. We have assessed the stability of CLZ/TAZ 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 YCD standards[1]. Initial pre-scoping work indicated that using pH buffered diluents did not provide any additional stability for CLZ/TAZ over 0.9% w/v saline as diluent and that at 32°C, the concentration of ceftolozane fell below the YCD limit of 95% of active remaining at the end of the infusion within 18 hours. As a result, testing was performed in 0.9% w/v saline and the "in use" infusion time was chosen as 12 hours. Testing was extended beyond the "in use" period of 12 hours in order to improve the accuracy of the data during the "in-use" period. Degradation kinetics for both devices at 32°C within the 95% confidence interval was performed. Data was processed using all five time points during the "in-use" period and statistical analysis performed to identify the optimum shelf-life.

METHODS

CLZ/TAZ was reconstituted and diluted in 0.9% w/v saline pH 7.0 at two therapeutic concentrations of the drug combination (5 mg/mL and 20 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 8 days, followed by a 3-hour warm up period at room temperature and a 12-hour simulated infusion period at 32°C. Concentrations of CLZ/TAZ were determined using a stability indicating HPLC-DAD method developed by BSTL for use in this study. Testing was carried out using triplicate devices for each of the elastomeric pumps. Laboratory testing included subvisible particle counts, pH and visual appearance testing and HPLC-DAD analysis at five timepoints.

RESULTS

The general YCD limit of 95% - 105%[1] was applied to both ceftolozane and tazobactam (from the initial concentration remaining) as there is no British Pharmacopoeia monograph available for CLZ/TAZ solutions for injection.

HPLC-DAD analysis for CLZ/TAZ concentrations was performed at five time points during storage for 8 days fridge 2-8°C, 3-hour warm up and then 12-hours "in-use" at 32°C simulating administration (Figures 1 and 2).

This study is consistent with the pre-scoping stages of the study confirming that ceftolozane is significantly less chemically stable than tazobactam. Therefore, the reduction in concentration of ceftolozane during storage is the limiting factor responsible for determining the shelf-life of CLZ/TAZ solutions for infusion within the elastomeric device. At the end of the 18-hour testing period the concentration remaining for ceftolozane fell outside of the YCD acceptance limits at both 5 mg/mL (lower) and 20 mg/mL (upper) concentrations, in both devices.

The maximum shelf-life that could be assigned was for 8 days storage in fridge, 3 hour warm up and 12 hour administration period at 32°C. CLZ/TAZ solutions for injection comply with and remain above the YCD lower limit of the 95% plus confidence interval for both actives at the end of the administration period in both the FOLFusor LV10 (Baxter) and Easypump®II (B.Braun) elastomeric devices tested.

CONCLUSIONS

The data obtained supports assigning a shelf life of up to 8 days in fridge (2-8°C), using 3-hour warm up period and a 12-hour administration "in-use" period for CLZ/TAZ solutions for injection in both elastomeric devices tested.

HPLC-DAD assay results from this study show that ceftolozane, while relatively stable at fridge temperature, undergoes significant degradation during the administration "in-use" period at 32°C. Tazobactam, in contrast to ceftolozane, remains relatively stable even at 32°C. The ideal administration period for most OPAT services is 24 hours, which is convenient for daily clinic attendance, nursing visits to a patient's home or self-administration.

However, the outcomes from the stability study presented show that this is not possible for CLZ/TAZ and hence a 12-hour administration is required. For OPAT services using a two-pump model to provide 24-hour infusions of CLZ/TAZ this is viable and is supported by the drug stability data reported here.

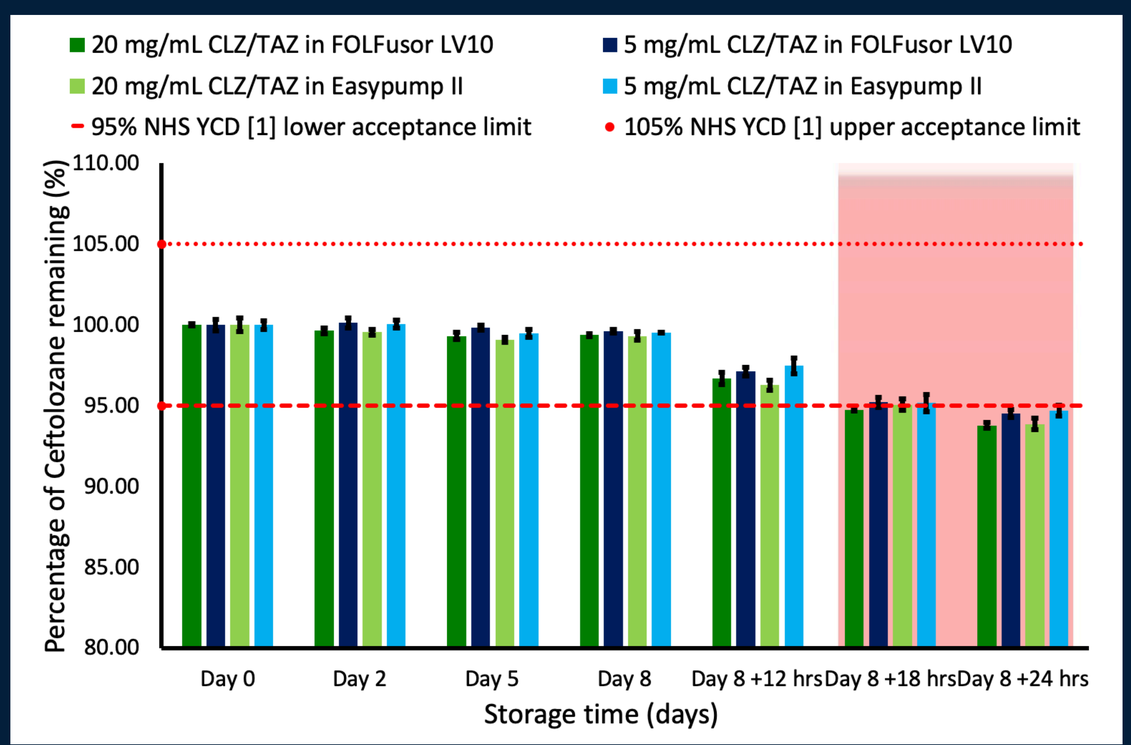

FIGURE 1. Ceftolozane remaining (%) versus time (days/hours) for FolFusor LV10 (Baxter) and Easypump II (B.Braun) devices.

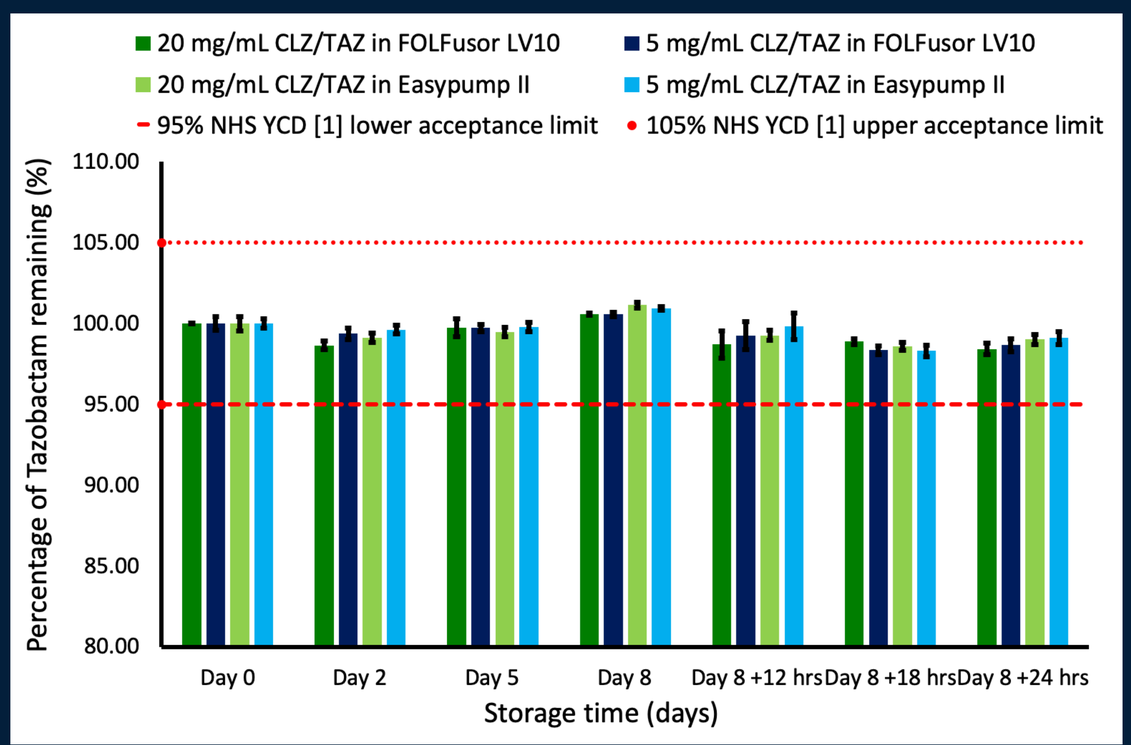

FIGURE 2. Tazobactam remaining (%) versus time (days/hours) for FolFusor LV10 (Baxter) and Easypump II (B.Braun) devices.

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ACKNOWLEDGEMENTS

This study was supported by: A Non-Clinical MISP Study Agreement from Merck Sharp & Dohme Ltd., UK (#57092), an Unrestricted Grant from B. Braun Medical Ltd., and consumables provided in-kind from B. Braun Medical Ltd. and Baxter Healthcare Ltd.

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