The Problem with PipTaz: Using Pharmaceutical Science to Provide Healthcare Solutions

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INTRODUCTION

The combined antibiotic treatment of Piperacillin and Tazobactam (Pip/ Taz) is widely used throughout Betsi Cadwaladr University Health Board (BCUHB). As piperacillin is a broad spectrum antibiotic and tazobactam helps overcome resistant bacteria this therapy treats a range of indications and is frequently given by Accident and Emergency Departments [1]. With an average annual usage of approximately 130,000 doses, it is one of the most prescribed antibiotics in the Health Board.

Whilst the drug is invaluable to the Health Board, in a time of stretched resources and increasing expectation the drug poses one significant issue – it's reconstitution time. Each dose of Pip/ Taz takes approximately 15 minutes to reconstitute and prepare by a nurse, and as the average patient requires 3 doses per day this is a significant drain on nursing time.

Many hospitals nationwide have a Pharmacy Technical Services team comprising of Aseptic Manufacturing Facilities and Pharmaceutical Laboratories. Within Wrexham Maelor Hospital the facility holds an MHRA specials license enabling large scale batched manufacture of ready to administer pharmaceuticals. In this work we look to demonstrate proof of concept that the aseptic unit can manufacture ready to administer Pip/ Taz doses to save nurse time and improve hospital flow in a sustainable way.

METHODS

This proof of concept work comprises 3 sections.

Analytical Method Development

A High Performance Liquid Chromatography (HPLC) method will be developed to simultaneously analyse both piperacillin and tazobactam and to determine the content assay for both active ingredients and related substances. It will be developed in accordance with the guidelines set out by the International Conference for Harmonisation [2].

Stability Studies

Stability studies are to be carried out in accordance to the NHS Yellow Cover Document (YCD) for small molecule drug stability [3]. The drug product to be assessed will be 4.5g Piperacillin/ Tazobactam in 120 mL 0.9% Sodium chloride as used on the wards within BCUHB.

Production Process Development

A semi-automated production method utilising bulk pharmaceutical intermediates will be validated.

RESULTS

HPLC Method Development

A stability-indicating analytical method was developed, demonstrating linearity across a concentration range of 0.1 mg/mL to 1.5 mg/mL. Impurities listed in the BP are detectable at concentrations above 0.04 mg/mL, with baseline resolution achieved between active peaks. A run time of 15 minutes makes this suitable for high volume analysis within the laboratory.

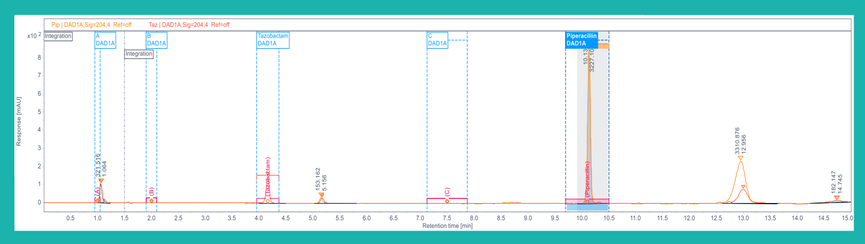


Table 1: Estimated Time for production

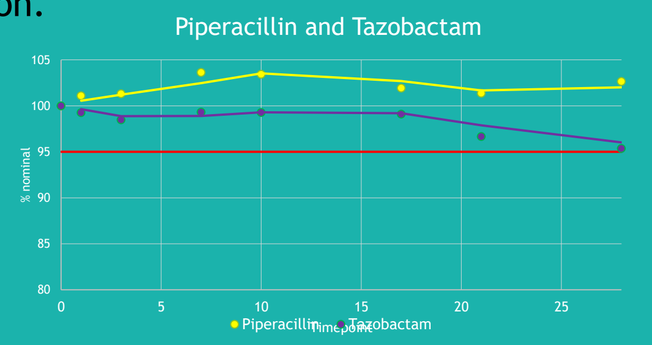
Method of preparation	Preparation of 49 bags (minutes)	Nursing/ operator time saved per batch compared to slowest method (minutes)
Nurses on wards	735	0
Aseptic - manual	240	495
Aseptic - automatic	45	690

Time Studies and Manufacturing Validation

A manufacturing method utilising an IMF Vigo peristaltic pump and AddedPharma Pip/ Taz Smartpak yielded 49 ready to administer drug products within 45 minutes. The average Piperacillin and Tazobactam concentrations that were within 3.5% of the target nominal concentrations of 0.6675 mg/mL and 0.0825 mg/mL respectively. Time in motion studies were conducted on the old manual aseptic manufacturing process and a time saving of approximately 94% had been made by utilising automation.

Manufacturing Development and Stability Study

The stability study evaluated the following product parameters; appearance, pH, sub-visible particle count, assay, and related substances. The appearance, pH, and particle counts remained within the specification limits for Piperacillin and Tazobactam infusion preparations for the entire study. At day 28 the Tazobactam assay failed with an increase in variability between individual injections and assay results as low as 90.7%. The assignable shelf life at 5°C ± 1 °C is **21 days**.



DISCUSSION

The work to date on this project indicates that the implementation of new automation technologies and the utilisation of new bulk pharmaceutical intermediates into Pharmacy Technical Services can be used to help overcome some of the challenges faced in a modern healthcare environment.

Data provided by the BCUHB analytics team shows that approximately 130,000 PipTaz vials were issued to wards for use in patients across BCUHB during 2024. Each of these vials requires dissolution prior to use, significantly impacting nursing time across an entire year, with an average preparation time of 15 minutes per vial on a ward a maximum 32,500 nursing hours could be saved should 100% of the production be moved into Pharmacy Technical Services.

Whilst this is not likely attainable with current capacity in the Technical Services team even meeting 10 – 20% of the demand would have a significant impact on available nursing time and patient flow within the hospitals of BCUHB.

FURTHER WORK

This proof of concept study demonstrates the advantages of this manufacturing method over both the methods currently used by Pharmacy Technical Services and ward preparation. During the next 6 months the Technical Services team within BCUHB will look to realise this proof of concept work into a full scale manufacturing environment with product delivery to patients. We will look to conduct stability studies on an alternative formulation historically used by BCUHB using a 5% glucose solution diluent.

REFERENCES

1. Piptaz - NPS MedicineWise; www.nps.org.au/medicine-finder/piptaz-powder-for-infusion
2. International Conference for Harmonisation. (2003). Analytical Method Validation 'Q2'.
3. NHS Pharmaceutical Quality Assurance Committee. (2019). A standard protocol for deriving and assessment of stability 5th Edition 'Part 1 – (Aseptic Preparation - Small Molecules)'.

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