The Role of Technical Services in Improving Access to OPAT in North Wales

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Introduction

What is OPAT?

OPAT is Outpatient Parenteral Antimicrobial Therapy, this treatment facilitates patients to receive intravenous antibiotics in their own home. By enabling this OPAT can improve the patient experience, reduce strain on family and friends and reduce exposure to co-morbidities often associated with lengthy hospital stays. For a healthcare provider there are many advantages these include improvements to patient flow, the release of nursing time, additional bed days and reduced costs. However despite the advantages for patients healthcare providers uptake in the UK has been slow due to clinical, financial and logistical concerns (1). Much work has been carried out to help minimise clinical concerns (2), yet due to the high risk, difficulty and time intensive nature of producing the filled elastomeric devices required provision of this treatment is reliant on Contract Manufacturers. This is costly, introduces a delay between prescription and treatment, and as recently demonstrated does not have a robust or reactive supply chain with lead times often longer than treatment times which reduces confidence in the service.

What do we want to do?

Technical Services departments are well placed in order to help over come some of these barriers to starting an effective OPAT service and improving access to existing ones, by using the skills and knowledge developed over years of CIVAS provision. Furthermore automation is becoming more affordable and suitable for use in aseptic units and offers the chance to batch manufacture devices thus decreasing the manufacturing times of devices and reducing the strain on aseptic manufacturing technicians. Additionally most commercially available products are supplied with a 13 day refrigerated and 1 day 32°C shelf life, this shelf life is not conducive to the long term storage of treatment courses and limits the availability of the devices with manufacture required after a prescription is received. If the shelf life was extended then dose could be prepared and stored within the pharmacy so they are ready when a patient requires them.

AIMS AND OBJECTIVE

The aim of work was to determine whether Technical Services in Betsi Cadwaladwr University Health Board could overcome the following challenges facing delivery of an OPAT service:

1. High cost of treatment
2. High lead times and lack of supplier contingency
3. Difficulty of filling the elastomeric devices

The objectives were as follows:

1. Develop a semi-automated method to manufacture doses
2. Carry out stability studies to extend the current shelf life offered by suppliers

In order to carry out this proof of concept study the work was centred around the manufacture of 8g/ 240 mL flucloxacillin elastomeric devices. This drug product had been identified by the Health Board's antimicrobial pharmacists as been the most widely used OPAT suitable antibiotic in use within BCUHB.

METHOD

Advantages of Automation

Time studies were carried out whereby production of equivalent batches using current manual aseptic manufacturing techniques and semi-automated manufacturing method were timed.

HPLC Method Development

A stability indicating method, developed in accordance with ICH Q2.

Figure 1: Grifols Gri-Fill 4

Stability Study

Stability studies were carried out in accordance with the guidance set out in the NHS Yellow Cover Document. Batches of 8g/ 240 mL flucloxacillin in 0.9% citrate buffered saline were manufactured using EasyFlow (Adriamed, Pescara) and Easypump II (B Braun, Melsungen) elastomeric devices. These were stored under the following conditions: 4°C, 25°C/ 40%, and 32°C 60%. The study was conducted until the testable product is depleted or 2 time points after the degradation limit was reached

CONCLUSION

This study into the use of semi automated in-house manufacture of elastomeric devices for OPAT within technical services can realise the following benefits:

- **Manufacture devices in less than 20% of the time when compared to traditional manual methods**
- **Increased shelf life when compared to commercially available products, over 300% when refrigerated.**
- **Manufacture doses for 30% the cost of commercial purchase**
- **Reduce time to dose from 24 hours to 0 hours.**

RESULTS

HPLC Method Development

An analytical method was developed that was shown to be stability indicating. It is linear across a concentration range of 0.002 g/mL to 0.066 g/ mL. All impurities given in the BP are detectable to 0.002 g/mL with baselines resolution to the primary flucloxacillin peak

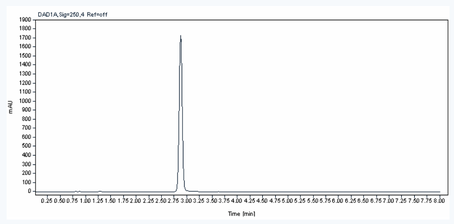


Figure 2: Sample flucloxacillin chromatogram

Table 1: Flucloxacillin Stability Indicating HPLC Method Parameters	
Run Time	8.00 minutes
Wavelength	250 nm
Flow Rate	1.0 mL/ min
Injection volume	5.0 µL
Column	C18 100 x 4.6 mm 2.6 µm 100 Å
Mobile Phase A	Acetonitrile
Mobile Phase B	10 mM di-sodium orthophosphate pH 2.5
Column Temperature	30.0 °C
Needle Wash	Methanol

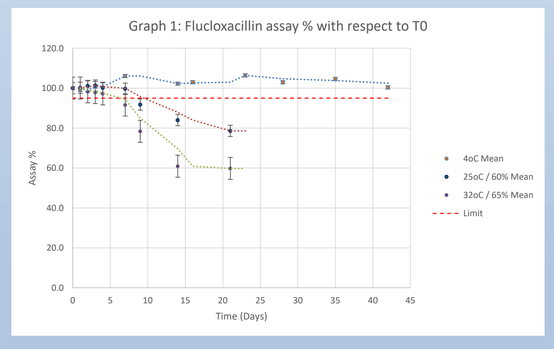
Time Studies and Manufacturing Validation

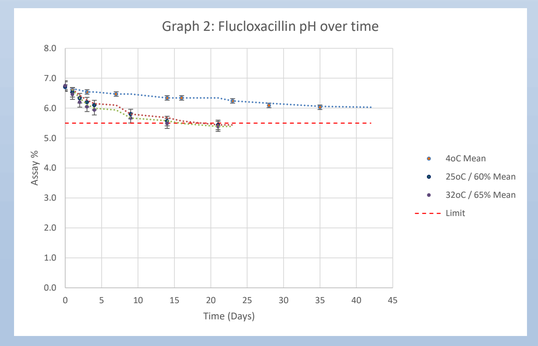
The manufacturing method using the Gri-Fill was found to produce devices with an average concentration of 0.33 g/mL (RSD% = 2.8%) with an average fill volume of 240 mL (RSD% = 0.35%). Operators were timed when manufacturing batches devices for OPAT using manual techniques and when using the Gri-Fill 4. The average approximate timings to prepare one batch of 4 devices are given below:

- Manual filling: 5 hours
- Semi-Automated filling: 45 minutes

Manufacturing Development and Stability Study

Throughout the stability study the appearance, pH, sub visible particle count, assay and related substances have been assessed (n=4 for each storage condition).





Appearance, pH and particle counts were all within the limits outlined by the British pharmacopoeia for flucloxacillin injectable preparations. Assignable shelf lives at each storage condition at the conclusion of this study are:

- 4°C: 42 days
- 25°C/ 40%: 9 days
- 32°C 60%.: 4 days

IMPACT

By utilising the latest automated filling technologies and the available expertise of a Trust or Health Board's Technical Services team, it is possible to produce filled elastomeric devices within a hospital's aseptic units. This provides an effective solution to overcoming many of the barriers to the wider adoption of OPAT services within the UK and making the devices more accessible by reducing costs and reliance on contract manufacturers. Additionally the extended shelf lives now assignable to the elastomeric devices filled within BCUHB can enable them to be prepared in advance of requirement and held as a 'stock item' within the hospital pharmacy further reducing the time from prescription to treatment. The table below looks at estimates of the cost of treatment for three methods of IV flucloxacillin delivery, assuming a best case scenario for delivery from a contract manufacturer.

Table 2: Estimated Cost of Treatments				
Method of Treatment	**Days in Hospital**	**Cost of Stay (£)**	**Cost of Treatment (£)**	**Total Cost of Patient (£)**
In - Patient	14	7490	490.00	7980.00
Contract Manufacture OPAT	1	535	1613.50	2148.50
Technical Services OPAT	0	0	494.00	494.00

By enabling the spread and scale of OPAT services further benefits can be can be realised through the healthcare environment allowing for better patient experiences and clinical outcomes. The additional bed bays released through early discharge on OPAT, enables patients with greater healthcare requirements to receive the treatment they need. Feedback and questionnaires carried out on OPAT patients within BCUHB demonstrate that the OPAT patient is provided greater quality of life without diminishing the quality of treatment. With all of these factors considered OPAT is well suited to the plan set in the A Healthier Wales: Our Plan for Health and Social Care [3] document published by Welsh Government.

References

1. Chapman, ALN. (2013). 'Outpatient parenteral antimicrobial therapy clinical review', BMJ, 346.
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3. Welsh Government – A Healthier Wales: Our Plan for Health and Social Care. https://www.basw.co.uk/system/files/resources/180608healthier-wales-mainen.pdf

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