

**Guidance on the Pharmaceutical Issues
concerning OPAT
(Outpatient Parenteral Antibiotic Therapy)
Services and other
Outpatient Intravenous Therapies**

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Overview

The development of OPAT (Outpatient Parenteral Antibiotic Therapy) services and other outpatient intravenous therapies has been rapid over recent years and there are many models of service development.

It is likely that these services will continue to develop in order to reduce the burden on hospital beds and to improve quality of care and patient outcomes.

The pharmaceutical aspects of these services have not always been considered, this document aims to address some of these issues to ensure that the services provide safe and efficacious treatments which fully meet with patient needs.

The areas covered include considerations for drug stability particularly considering the temperatures during extended infusion times. Related to this there is guidance for patients on how to handle their infusers during storage and during the infusion period to prevent the product being subject to excessive temperatures.

There is also discussion on the use of buffers to stabilise certain drugs and considerations for ensuring mixing of drug and diluent, if this is carried out within the device.

Intended audience:

This document is intended as a reference and source of information to the following audiences:

- Antimicrobial pharmacists
- Medical microbiologists
- Infectious Diseases physicians
- OPAT nurses
- Procurement specialists

The above staff groups may not be acquainted with the requirements/pharmaceutical considerations of drug stability testing and the quality assurance of pharmaceutical products;

- Quality Assurance
- Technical staff
- Aseptic staff

The above staff groups may not be familiar with OPAT services and have a need to gain an insight into the clinical/microbiological requirements of these services, and be aware of the BSAC Good Practice guidelines and BSAC DST scheme

- Chief pharmacists and
- Medical directors

The above staff need to provide assurance that the pharmaceutical preparations prepared or procured and supplied by pharmacy departments are fit for purpose and are being stored, administered and monitored in a clinical service that is safe and effective and that pharmaceutical governance requirements are met along with clinical governance requirements.

Introduction

Outpatient intravenous antimicrobial therapy (OPAT) is an increasingly used means of treating patients who need long courses of intravenous antibiotics, but who do not need to stay in hospital. OPAT services across the UK are growing in both number and complexity, and there is no single model of care. Drivers for OPAT services in the NHS in 2018 include reducing the length of patient stay in hospital to increase capacity within the system, a faster patient recovery free from the risks of hospital acquired infections, an overall improvement in the quality of care and improved cost effectiveness of treatment.

In 2012, the British Society of Antimicrobial Chemotherapy published good practice guidelines¹ for the development of OPAT services, which outlined the basic requirements for OPAT services in terms of governance arrangements etc. and were mainly aimed at those interested in setting up OPAT services and those involved running the services (e.g. medical microbiologists, infectious diseases physicians, antimicrobial pharmacists). To date, less attention has been paid to the pharmaceutical requirements of OPAT services, in terms of drug stability testing etc. The consequences of not considering these issues include reduced efficacy & cost-effectiveness of treatment, increased risk of toxicity and avoidable safety risks, potentially impacting on the antimicrobial stewardship agenda.

The development of OPAT services has usually been led by these clinicians, in conjunction with hospital managers and commissioners; specialists in drug stability and quality assurance of pharmaceutical products have generally not been involved or consulted at the early stages of developing services. The clinical staff listed above will not usually have sufficient training or awareness of the pharmaceutical considerations of drug stability testing, assurance/certification/QA processes to ask the right questions of device suppliers/providers of compounded preparations in devices/syringes/bags. The early involvement of technical/aseptic services staff can have benefits for OPAT services in being able to fully assess the range of drugs/devices that are available to the service, support the selection of suitable agents and devices to meet the needs of the service and ensure that the relevant standards for pharmaceuticals have been met.

OPAT services in the UK are currently fragmented – there is no single model for delivering care to patients; OPAT services can be delivered in patients' homes, in community clinics or hospital clinics. OPAT services have usually evolved based on the constraints of the healthcare provider – either in terms of staff available to manage and run the service, or within the boundaries set by the commissioners of the service. The case mix of the healthcare provider often influences the design of the service as well. Another factor that is relevant to OPAT services in terms of their evolution and design/delivery is the range of drugs available to use within the service and their mode of administration to the patient. Many services will use drugs which can be freshly prepared in the clinic or a patient's home and administered by bolus injection or short infusion. While this can be the ideal in terms of drug stability, it can limit services to using only those drugs which can be administered in this fashion and as a consequence, may limit the range of infections that can be treated via OPAT; in addition, the evidence base for using these convenient agents may not be as strong as for those agents whose administration would be more difficult in an OPAT setting

(hence having a clinical impact on patient care). The increasing availability of products in devices which can administer the drug over an extended period of time has great potential for benefit, with respect to increasing the range of drugs that can be given and the infections treated as well as potentially maximizing Pharmacokinetics / Pharmacodynamics (PK/PD) for drugs such as beta-lactam antibiotics, making use of more narrow spectrum agents which can limit collateral damage and resistance development, possibly giving less drug to achieve the same outcome, reduced side effects, toxicity and drug acquisition costs.

In situations where problems with drug resistance has meant that OPAT services have needed to use broad spectrum agents (or conversely, when narrow spectrum agents are being used preferentially) and these agents have a requirement to be given by a prolonged infusion, there is often no published data to establish whether the drug is stable when given as a prolonged infusion. This has in some situations led to the reliance on commercial providers who can try to provide assurance of stability – but now there is increasing awareness of the need to meet the NHS YCD (Yellow Cover Document)² requirements in terms of the data; there is limited (or no) availability of open access data that could allow widespread compounding of these agents in NHS licensed facilities. It was as a result of this that BSAC (British Society for Antimicrobial Chemotherapy) established the Drug Stability Testing programme to support the OPAT community.

The principles of this document can be applied to the broader area of all IV infusions of small molecule drugs given in or provided for the homecare setting including cytotoxic chemotherapy, desferrioxamine etc.

Drug Stability

It is important that the stability of the drug solution is fully understood before its suitability for OPAT services can be assessed. The NHS YCD² should be consulted for information on stability testing and assessment of stability data but the following specific principles apply to OPAT services

- Stability trials must include the storage period in a refrigerator together with assessment of the infusion time if this is in excess of one hour and for ambulatory infusers or other ambulatory delivery, this should be carried out at 32°C or above, as studies have shown that this is the temperature of solutions administered via an infusor next to the body.
- Sequential studies are recommended where the stability trials follow the product in the refrigerated storage followed by the in-use period
- Stability studies must include a stability indicating assay, analysis and understanding of degradation products, physical examination of solutions for significant changes, sub-visible particle counts and pH as a minimum. The expiry period can be limited by the increased presence of a toxic degradant even when the active assay is still within its specifications

- Data should not be extrapolated outside of the conditions of the study, without expert interpretation and full knowledge and understanding of the product and components for example the drug concentration must be within those studied and shown to be stable,
- Any data or studies not fully compliant with the YCD² must be fully risk assessed for suitability before that data is used to support a product shelf life.
- Note that where there is a British Pharmacopoeia (BP) monograph for a product the product must be compliant with this monograph throughout its shelf-life.

Use of buffers

In order to provide a product stable enough for extended (up to 24 hour) infusion periods some products have been stabilized with a buffer during stability trials. If these products are to be used then they must be buffered using the same buffering system and to the same pH as was used in the stability trial. Clearly adding the correct quantity of buffer is critical to producing a stable product and this does add complexity to the compounding process. In these cases it is clearly advantageous for the product to be compounded within a controlled aseptic unit environment. If these products need to be made up at the bedside then it is recommended that a buffered saline of the correct concentration is provided to nursing staff with the product concerned.

Any clinical impact of the buffering system used also needs to be considered, for example, citrate if it is not adequately metabolised by the liver may bind to calcium leading to hypocalcaemia, however, at the concentrations used this would not be expected to have an impact for a majority of patients.

Other Compounding Issues

For products compounded within aseptic units consideration of the preparation time and the time that a product spends out of the refrigerator following preparation should be considered in terms of its impact on drug stability.

Wherever compounding takes place, the use of elastomeric devices requires assurance regarding mixing of the drug with the diluent. Most commercially available elastomeric devices consist of a protective hard plastic outer case enclosing a flexible inner balloon containing the medicine and diluent for administration. There is no or little air within the inner balloon so it is difficult to mix the product in the device by shaking. Hence mixing is reliant on the properties of the device, if this is not fully understood then mixing of drug and diluent should take place ahead of filling, taking care to use closed systems. An alternative approach may be to add aliquots of diluent and drug although this makes the filling process more complex and should be restricted to aseptic services units.

Assuming that the device manufacturer can provide evidence of mixing in the device then the diluent should always be added first followed by the drug solution. There is a possibility for less stable drugs that infusers filled with diluent can be supplied for the drug to be added later, but this must only be considered where mixing in the device has been fully validated.

Poor mixing of the medicine and diluent could lead to inconsistent dosing of drug throughout the infusion period, could affect both chemical and physical stability of the drug and may cause local irritation at the administration site.

Procurement Issues

Ready to administer products will generally be manufactured under a Manufacturer's Specials Licence and hence will be unlicensed products. It is the responsibility of the procurement pharmacist to assure that the product is of a suitable quality and is otherwise suitable for the patient, including being stable for the storage period and expected infusion period. Stability data or references should be obtained from the supplier and compared against the standards in the YCD² which contains an assessment template for evaluation of suppliers' stability data. For in-use periods in excess of one hour this must have been assessed during the stability trial at a 32°C or above for elastomeric devices worn by the patient, for other devices with less insulation then a higher in-use temperature may be appropriate. If the infusion container is away from the patient then room temperature may be justified for the in-use period (25°C).

Where applicable cold chain must be maintained throughout the transport of the product from the manufacturer to the patient in order to maintain stability. Products can be removed from the refrigerator for up to 30 minutes prior to the start of infusion to allow warming of the solution for patient comfort and also to ensure accuracy of the infusers.

Storage Issues

Unless otherwise stated all antibiotics compounded ready for administration must be stored in a refrigerator (2-8°C) and protected from light. It is important that cold chain integrity is maintained throughout the supply chain until the product is removed from the refrigerator ahead of administration to the patient. Refrigerators used must be capable of maintaining a temperature between 2 and 8°C including those for storage in the patients home. Refrigerators should be monitored for compliance with this standard and any temperature excursions need to be risk assessed in terms of impact on product suitability for use. The product supplier should be consulted as part of this risk assessment process.

Administration Issues

For elastomeric devices, in order that an accurate administration flow rate is maintained the device should generally be kept at heart height, although this may

differ for specific devices and manufacturers information should be consulted, if the device is held higher than specified it may infuse more quickly and if lower it may be infused more slowly. This can be critical for 24 hour continuous infusions to ensure correct dosing.

Temperature is a critical parameter for the stability of medicines. The Arrhenius equation shows that for every 10°C rise in temperature there is a doubling of the reaction kinetics and hence the degradation rate. Product degradation not only reduces the amount of available drug but will also produce degradation products which in some cases may be toxic. They may also cause significant physical changes in products such as precipitations and colour changes.

The temperature of elastomeric devices worn on the body has been assessed in various studies^{3,4,5} and these give an insight into good (and bad) practice for wearing such devices for antibiotic infusions, particularly 24 hour continuous infusions. If devices are handled appropriately then it is likely that the solutions within them will remain below 32°C, which is the temperature at which stability studies have been conducted. This will ensure the product remains compliant with standards throughout the administration period.

It is vitally important that devices are not placed / kept in direct sunlight as this can lead to excessive heating of the device; (temperatures in the range of 43°C have been recorded⁴) - this will have a significant impact on drug stability. Furthermore where the device is kept at night has a fundamental impact on the temperatures to which the drug solution is exposed⁴. Devices stored on the bed (above the pillow) or away from the bed maintained a suitable temperature throughout the night and in fact the temperatures fell overnight. Devices stored at night on the body and hence under the bedclothes did show an increase in temperature overnight at could exceed the 32°C assessed for stability.

It is therefore paramount that patients are informed to keep the infusor out from under the bedclothes at night and also not to expose the infusor to direct sunlight even if it is stored within a pouch.

Current Gaps in Knowledge

Understanding and development of the optimal method mixing of antimicrobials following dilution and loading into the various elastomeric devices. The full clinical impact of the buffering systems used needs to be assessed over time (see below).

Pharmacovigilance

In line with other medicines it is important that any Adverse Drug Reactions (ADRs) are reported in accordance with the Yellow Card reporting scheme and the fact that the product is a compounded Special and whether or not it has been buffered should be captured within the report to allow efficient trending of issues. Any issues should also be reported to the Specials Manufacturer or aseptic compounding unit who provided the product.

Other considerations (Q&As):

Q. *What is the role of device manufacturers and the pharmaceutical industry in OPAT?*

- A. The aseptic compounding community within the NHS and private sector has a responsibility to provide robust products which will be practical and suitable for use and with carry a suitable and robust shelf-life to enable appropriate use including for extended infusion times where required.

Device manufacturers need to ensure that there is suitable drug stability data presented to users for each drug formulation that will be filled into the infuser. Ideally this should be specific to their infuser; if the data is extrapolated from another product then justification must be given in terms of the suitability and comparability of drug solution contact materials.

This data should cover storage for products to be compounded in advance in pharmacy aseptic units as well as to cover any administration period whenever the product is made up. The standards referenced above should be followed.

Q. *What questions should providers of OPAT services ask of providers of devices/compounded drugs/new drugs to market?*

- A. They should request to see the stability data for all drugs that they wish to use in the device, this should not just be a table but should contain references to the original studies and ideally these studies should be reviewed or assurance obtained that an independent peer review of the studies has been carried out against the YCD requirements.

They should also check that the infuser has been CE marked as a Medical Device for sale within the EU, and whether the supplier can provide evidence as to whether drug solution and diluent can be mixed in the infuser or whether it should be mixed in advance of filling the infuser. This may be supplied as video evidence of mixing using a coloured dye or a laboratory exercise to demonstrate a suitable level of mixing when the drug is added to the pre-filled diluent.

Q *Are all elastomeric infusers the same and can data be extrapolated between them?*

- A. They are not all the same. There are significant differences in the drug contact components particularly the elastomeric balloon. Extrapolation of stability data to other devices to those tested does need a degree of expertise and understanding of both the drug and the properties of the device.

Different elastomeric infusers may also have different temperature profiles in-use due to the varying degree of insulation between the outer case and the solution and also the materials used in construction. In general providing the

instructions above are followed regarding stability studies and handling then this should not normally present a problem.

References

1. Good Practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. *Journal of Antimicrobial Chemotherapy* 2012; 67:1053-1062 Chapman et al,
2. A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (Small molecules) Edition 4 (April 2017) NHSPQA Committee
3. What is the maximum temperature reached in elastomeric devices under simulated OPAT conditions? *Archives of Disease in Childhood*. 101(9), p.e2. van Der Merwe, S. and Green, H. (2016) . Poster presented at NPPG November 2015
4. Antibiotic stability related to temperature variations in elastomeric pumps used for outpatient parenteral antimicrobial therapy (OPAT). *J Antimicrob Chemother* dkw582 Rachel Voumard, Niklas van Neygham, Camille Cochet, Celine Gardiol, Laurent Decosterd, Thierry Buclin, Serge de Valliere
5. Temperature profiles of antibiotic-containing elastomeric infusion devices used by ambulatory care patients, *AM J HEALTH-SYST PHARM* Volume 74 Number 13, 992-1001, Toni Docherty, Michael Montalto, Joni Leslie, Katrina King, Suzanne Niblett, Tim Garrett