Vision paper on the future of pharmacy technical services and the provision of patient specific parenteral chemotherapy treatments

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Abstract

Despite major changes in available technology, aspects of pharmacy technical services relating to chemotherapy preparation and administration have not changed significantly in the last 10 years. Improved processes for preparation and administration of chemotherapy and the advent of dose banding with batch preparation have facilitated further development of cancer services provision within the UK. However, advances in cancer therapy, e.g. development of monoclonal antibodies and tyrosine kinase inhibitors, have also increased the complexity of demands on pharmacy chemotherapy services, which coupled with improved cancer patient survival, continues to place increased demands for chemotherapy services.

The aim of this paper is to stimulate debate by outlining not just the current position and limitations but looking to potential future developments. Options, not constrained by professional considerations, current technological or resource limitations are discussed. As such this paper should not be seen as the only option, but merely to stimulate consideration of ways of smarter working and evolution in our roles and responsibilities.

Keywords

Chemotherapy, dose banding, preparation and administration, technology

Process and technology advances in pharmacy technical services

The number of new cancer cases per year in England is predicted to increase by 33%, from 224,000 in 2001 to 299,000 in 2020 [1]. Chemotherapy activity continues to increase with the anticipated burden of cancer expected to increase at a rate of around 60% in four years [2].

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Chemotherapy drugs are inherently hazardous, requiring careful and safe handling to minimise occupational exposure of healthcare professionals. The National Institute for Occupational Safety and Health [3] has developed a knowledge base on safe exposure limits and in the UK the use of externally vented negative pressure isolators for the preparation of chemotherapy has helped to reduce exposure risk and promote safe handling. Most recently automated (robotic) preparation has become a focus of interest. At the same time safe handling guidelines and the use of closed systems for preparation and administration have been developed [4].

Parenteral chemotherapy must be prepared in environmentally controlled conditions in pharmacy. Aseptic preparation units face the challenge of continuing to deliver chemotherapy in an efficient, safe and economic manner, producing a product fit for purpose whilst keeping pace with innovation, rapidly rising demand, clinical and pharmaceuticals development.

Developments discussed below have all occurred with three main aims in mind: increased efficiency, increased patient safety and reduced patient waiting time.

Dosing options

The use of body surface area (BSA) in chemotherapy dosing has been established in clinical oncology for

over 50 years and has its basis in an original paper by Pinkel [5]—subsequently utilised by Freireich et al. [6]. The original BSA calculation investigation by Dubois and Dubois [7] was based on a sample of only nine individuals (two of whom were probably deformed) and its use for the early part of the 20th century was confined to animal studies for the purposes of inter-species scaling of toxicology data in phase I studies of anticancer drugs. To date, the Dubois and Dubois equation has been subject to much debate and other methods of BSA calculation [8, 9] have been proposed. However, the Dubois and Dubois equation remains the most commonly used system of BSA calculation in chemotherapy dosing in the UK.

In addition to BSA, there are many other factors that introduce further variability in chemotherapy dosing [10]. Cachectic or obese patients and elderly or paediatric patients reflect the population extremes where further variability is more likely. Similar considerations apply to paediatric patients.

For drugs dosed according to renal function a similar choice of formulae exist, and for dose calculating carboplatin, there is a choice between Cockcroft and Gault formulae [11] or the Wright equation [12]. In terms of dose modification the latest version of the *British National Formulary* suggests using the Modification of Diet in Renal Disease (MDRD) formula [13]. This is in direct contrast to the stance taken by FDA which requires dose adjustment to be based on values calculated using Cockcroft and Gault formulae. For clinical trials, the authors are unaware of the use of MDRD equation to calculate renal function estimates to be used to determine dose modification.

Chemotherapy dosing has traditionally been individualised with a view to maximising therapeutic benefit and minimising toxicity in chemotherapy drugs with a narrow therapeutic index. BSA has poor correlation to toxicity of drugs in humans [14]. The acceptance of variable dosing using BSA is far from universal as demonstrated by the interest in flat dosing [15, 16]. Opponents of BSA-based chemotherapy dosing have also suggested adoption of fixed doses of drug in BSA clusters [17, 18]. A review by Mathijssen et al. [19] considered flat fixed dosing in adults on the basis that the use of BSA does not reduce the inter-individual variation of adult pharmacokinetics. This pragmatic approach to dosing is based on the assumption that the known chemotherapy dose delivered to the tumour site (dose density) is subject to inter-patient variability and therefore variable therapeutic outcomes and toxicity levels in patient populations.

Whole vial dosing [20] too has been proposed using a similar argument to fixed dosing with the aim of helping manage pharmacy aseptic unit capacity.

In addition to BSA, there are many other factors that introduce further variability in chemotherapy dosing [21]. Uncertainty of measurement is also a well-documented concept. Measurement of height and weight has been suggested to vary by ± 10%. There is also a lack of consensus on the frequency of re-measurement of height and weight and the relevance of weight changes during chemotherapy treatment. Inherent inaccuracies in methods of height and weight determination in clinical settings, e.g. lack of standardisation, calibration errors on scales, variable techniques, also introduce unquantified variance. These variances all add multiple random errors to the chemotherapy dosing process. Table 1 below further illustrates these multiple sources of variability in chemotherapy dosing.

Dose banding

Dose standardisation and rationalisation is perceived in the UK to be essential to manage capacity as well as having economic benefits and promoting safer prescribing. Dose banding has been used in practice since the late 1990s [22-24], yet is still to be universally accepted.

Batch preparation of chemotherapy was developed around dose banding but in the UK this has been limited to pharmacy preparation units holding Manufacturers' Specials Licences. The paucity of hospital pharmacy

Table 1: Potential sources of variability in chemotherapy dosing

Process	Potential variability	Example of sources of variability
Individual patient drug handling (pharmacokinetics and pharmacodynamics)	± 15% (population-based)	Pharmacogenetics, disease effects (hepatic/renal dysfunction), co-morbidities, etc.
Vial contents	± 15%	Manufacturer, vial type, aseptic dispensing technique, etc.
Weight, height, BSA and renal function assessment	± 10%	Shoes, clothes, time of day, calibration, BSA calculation methodology, renal function assessment methodology, etc.
Syringe use	± 5%	Type, manufacturer and size, e.g. 3 mL vs 50 mL size, user, etc.
Residual volumes during administration	± 5% (process dependent)	Filter adsorption, administration set, inadequate flushing, etc.

BSA: body surface area.

departments with Manufacturers' Specials Licences preparing chemotherapy has led to a growth in commercial chemotherapy compounding companies in the UK. This may be explained by the observation that whilst there are over 80 licensed NHS aseptic compounding units, most have capacity for limited (often only patient-specific) local service only.

The adoption of dose banding was made on assumption that treatment is unlikely to be compromised by rounding the dose to the nearest dose within ± 5% dose variance. This assumption was promoted because of the limited evidence around the use of BSA to calculate chemotherapy doses.

On the other hand, the licensed dose for drugs in chemotherapy treatments is normally based on clinical trial dosing methodology and has been derived in the context of single drug treatment only. Hence, dose banding is perceived to deviate from an evidence-based approach reflected in the trial findings. Whilst dose-banding has been accepted in some clinical trial protocols, there is need for a standardisation and rationalisation of chemotherapy dose-banding protocols and methodology to ensure that dose banding does not affect clinical outcomes.

It has been proposed that in the future, individual pharmacokinetic profiles, supported by pharmacogenomic profiling should be used to support high-dose adjuvant therapies; however high-dose therapies have thus far failed to demonstrate significant survival benefit [25].

It should be noted that oral agents *have to* be dose rounded, often to a much larger tolerance, to match the strength of the available tablets or capsules, e.g. etoposide and capecitabine where oral dosing is rounded by 10–15%. Increasing use of oral chemotherapy has increased the use of dose rounding and promoted the use of standardised doses. This has been demonstrated in the IV to oral dose conversion of vinorelbine. Within some clinical trials dose levels for a whole patient population for such oral agents may be limited to just three doses.

Centralisation of services

The Calman–Hine Report 1995 [26] examined cancer services, and proposed a restructuring of cancer services to achieve a more equitable level of access to specialist expertise in the UK. One of its key recommendations was to concentrate cancer care to specialist centres, and advocated the 'hub and spoke model'. In the UK a range of 'cancer plans' [27] have been published which have all identified increasing requirements for cancer treatment and built on the Calman–Hine Report in terms of service delivery models which reflected population needs.

The increasing requirement for cancer services led to the development of a NHS Modernisation Agency report which looked at capacity planning for chemotherapy services. C-PORT, Chemotherapy Planning Oncology Resource Tool [28] was subsequently developed and has been used in various settings to project and plan oncology capacity and demand. It is not, however, a real-time model and is limited to impact modelling.

Centralisation of services has been adopted in various models throughout the UK. In some centres, this has facilitated chemotherapy doses being prepared in batches in advance of the patient appointment. A Specials Manufacturing Licence allows the service to assign longer expiry to the aseptically prepared products where extended stability data is available. Where prescriptions are requested and clinically verified in advance of the patients' arrival and assessment there has been a reduced waiting time for patients with a consequential improvement in the patient experience [12].

Batch preparation

The aim of batch preparation is to increase the efficiency of aseptic preparation and allow preparation in advance to reduce patient waiting time. This has greatest benefit for products with significant preparation time, which if prepared on the day required can significantly impact on turn-around times. A critical requirement is the availability of high-quality extended stability data; many manufacturers are now able to provide such data which is a necessity for participating in NHS tenders.

When coupled with dose banding this can have significant savings, both financial in terms of in-process waste reduction and ability to reuse or issue prepared doses only when a need is confirmed. There is also benefit to be achieved from improved quality of service and improved quality of products prepared. This is because batching of products is mainly undertaken in licensed manufacturing units which comply with good manufacturing practice standards and processes managed within a quality system. Batched production in licensed facilities with final product testing with rigorous release processes has also helped to give an increased assurance of product quality and mitigation of risk, overcoming the perceived disadvantages of extra cost and delayed availability associated with such a process.

It is important to recognise that batch preparation will not apply to every dose band identified. It is best applied to the dose bands used most frequently. In the UK, the Section 10 exemption of the Medicines Act 1968, allows for pharmacists preparation of products. In this scenario, the benefits of batch preparation are not evident, because

of limited expiry dates permissible and risk of waste from advance preparation (and to reuse within the shorter timescales if necessary). The benefits of batch preparation within licensed units is that the longer expiry available minimises the risks associated with preparing in advance (particularly where used in conjunction with agreed dose bands) and subsequently wasting prepared product.

Commercial suppliers of unlicensed specials have made the most of extended stability of some chemotherapy drugs but this has not really been the case within the NHS. Section 10 units, unable to batch prepare are now in a position to take advantage of the growth in commercial suppliers (possibly also NHS licensed units) of dose-banded products and gain some of the efficiencies experienced by licensed aseptic units.

Extended stability

Methodology of the assay and study and hence the quality of the data varies significantly as does availability of stability data and its applicability, e.g. data generated for an original branded drug cannot be automatically applied to later generic formulations. Stability databases exist which aim to collate available literature and make available such data. What they do not do is assess the data in terms of applicability, methodology and quality as highlighted in Table 2 below.

Attempts have been made to standardise the provision of such data. Ownership and financial gain from such extended stability data and how that relates to non-profit making organisations such as the NHS is something which needs to be established.

The MEDUSA [30] monographs provide a good starting point for promoting standardised preparation and administration. Currently available sources of shelf life and stability information include Stabilis [31], Pro-file [32], local/regional databases, as well as data from pharmaceutical manufacturers.

The limitations to such information sources are that interpretation is down to the user and application to local circumstances and an inability to share widely, even within the NHS itself.

It is therefore fair to say that there is a need to develop a database which covers extended stability for chemotherapy utilising an 'expert review body' to facilitate acceptance of such data and where disagreements persist to commission further work. The British Pharmacopoeia Commission is facilitating this by developing stability indicating assays as standard.

Table 2: Factors affecting extended stability data studies

Pharmacopoeia standards	• US studies often based on *US Pharmacopoeia* • UK studies may use *British Pharmacopoeia* standards/European, NHS Pharmaceutical Quality Assurance Committee standards (Yellow stability guide), or ICH [29] standards for conducting studies
Presentation differences	• Administration via elastomeric devices versus bags, versus bolus • Lack of consensus on diluent/dilution (concentration) • Extrapolation from historic studies using polyvinyl chloride (PVC) containers
Methodology	• Lack of agreement on 95% or 90% as the end point • Studies which stop before end point reached/exceeded. Limits and identification of degradation products
Data source	• Commercial versus academic studies • Peer review of studies • Good laboratory practice compliance and reproducibility
Other	• Investment in undertaking such studies • Return on investment • Extended stability not needed by everyone (relevance to practice)

These advances in developing extended stability data acknowledge the impact of dose banding on the activities of commercial companies and the NHS who increasingly demand extended stability data as part of their purchasing activities.

Presentation of final product

In the UK, bolus dosing using syringes is preferred for vesicant chemotherapy drugs, e.g. Epirubicin. In Europe, infusion dosing is more common for the same. Similarly, a range of delivery devices, e.g. elasatomeric devices, ambulatory pumps have been used to deliver chemotherapy.

The presentation of the final product determines the mode of delivery and the shelf life required, if the drug and presentation is to be of practical benefit. For this reason it is vital that there is consensus and agreement on the choice of presentation. For example, the choice of infusion container, dilution and diluent are all factors leading to variability in choice of presentation used in chemotherapy delivery.

Agreement and consensus on the final presentation is essential to ensure that stability studies are undertaken to mimic practice and to promote rationalisation of chemotherapy.

Automated preparation

Automation in UK NHS pharmacy preparation units is not established and most dispensing is still undertaken by pharmacy staff trained in aseptic techniques, and use of barrier technology. Automation of chemotherapy preparation ranges from simple syringe filling devices to fully automated cabinets, with a range between these extremes.

The major developments in automation of chemotherapy dose preparation have included syringe filling devices and fully automated devices such as Cytocare and Riva. The fully automated devices are still in their infancy and require some further development before they provide the benefits hoped for from such automation. In our view, whilst these advances are welcomed and encouraged, until the range of chemotherapy is standardised and rationalised, there is not sufficient economy of scale achievable to make use of the potential of this technology.

Reduced in-process wastage (sessional use of vials), reduced repetitive strain injury risks and increased efficiency are only some of the benefits. However, if vials were supplied in 'ready-to-use' (RTU) sizes, automation of preparation may change accordingly.

Administration devices

Administration device technology has also progressed and smart pump technology now allows syringe and infusion bag administration to be automated, safely providing increased control and patient treatment capacity.

Smart pump technology has potential to administer part vials or more importantly to reconstitute and administer part vials, administer the contents of prefilled syringes or RTU infusion bags. This could yield significant savings in staff time and reduce the risk of reconstitution errors and repetitive strain injury to staff.

Errors related to programming of the pump could be minimised using radiofrequency identification (RFID) or bar code labelling for patient specific dosing. Such pumps can be used to more accurately administer doses, particularly 'bolus' doses, the administration time for which can range from seconds to 10 minutes (slow bolus).

Labelling

In addition the development of bar code technology and more recently RFID tags is beginning to reduce risks associated with the preparation and administration processes.

Bar code technology can already be used by automated preparation devices and has become a mainstay of transfusion checking process. Confirmation of patient identity using bar-coded wrist bands coupled with bar-coded patient specific product labels could be used to reduce the risk of administration errors. RFID labelling with smart pump reading could permit further personalisation and risk reduction, preventing wrong drug–wrong patient errors, ensuring correct sequencing and administration.

Potential chemotherapy delivery scenarios
(given either current or developing technology)

Current	Scenario 1	Scenario 2	Scenario 3
Manufacturers of chemotherapy drugs present the drugs as a range of licensed vial presentations, from which the pharmacy preparation unit dispenses individual doses	Parenteral chemotherapy doses are supplied as ready-to-use or ready-to-administer presentations by manufacturers of chemotherapy	Manufacturers supply a range of agreed licensed doses which cover all doses over a predefined BSA range including dose reductions	Manufacturers supply a range of agreed licensed doses which cover all doses over a predefined BSA range including dose reductions with the added utilisation of smart pump technology and the use of RFID labelling

Current service

Pharmacy technical services in the UK prepare doses of chemotherapy drugs to meet local dosing schedules, chemotherapy delivery models and demand. Centralised services such as those based around cancer centres have the advantage of economy of scale and have been at the forefront of adopting batch manufacture and dose banding. Chemotherapy doses are prepared in pharmacy utilising barrier technology such as negative pressure isolators and clean rooms to manage inherent risks in the manipulation of parenteral chemotherapy.

Manufacturers of chemotherapy drugs present the drugs as a range of licensed vial presentations, from which the pharmacy preparation unit dispenses individual doses. Frequently, multiple vials are required to prepare a single patient dose which increases risk to healthcare staff, e.g. increased risk of needle-stick injury, and inevitably result in some product wastage.

Scenario 1

Parenteral chemotherapy doses are supplied as RTU or ready-to-administer (RTA) presentations by manufacturers of chemotherapy, requiring minimal further pharmacy manipulation.

Pharmacy would be responsible for prescription verification and labelling for individual patients and release

to the chemotherapy administration area when clinically appropriate. Exceptions to the above will be where formulation and/or stability prevent use of licensed RTA products.

Advantages of scenario 1:

1. Some RTA presentations of patient doses would not require further handling and manipulation.
2. Reduces use of unlicensed specials in hospitals.
3. Reduce need to maintain Manufacturers' Specials Licences.
4. Reduced workload for aseptic units which could then concentrate on short expiry or high cost agents and ensuring most efficient preparation of these agents. Releases (scarce) capacity to make doses of other high risk injections.

Challenges to scenario 1 include:

1. Lack of consensus amongst healthcare professionals on presentations required in varied clinical settings.
2. Some products are unsuitable for presentation as RTA or RTU presentation due to inherent stability and presentation constraints of the drug.
3. Development costs—the small market size (in comparison to that for the majority of licensed medicines) and current NHS contracting frameworks are not conducive to any manufacturer investing in product development and regulatory approval for what may be relatively low market share and short-term contract.

We believe that some common chemotherapy preparations could nevertheless be presented as licensed RTU or RTA presentations. These include the most commonly used doses of dose banded drugs and drugs that may be flat dosed, i.e the dose given as a fixed dose in a population as opposed to dosing by BSA or weight. For example, Vincristine is now prepared and administered as 1 mg and 2 mg infusion bags in 50 mL sodium chloride 0.9%. This could be made available as a licensed RTU or RTA presentation.

In addition, consideration needs to be given to awarding longer term contracts (5–10 years) to encourage companies to develop these products. The corollary to this is that for 'new' generic drugs the UK market is so volatile that the tendering process is encouraged to hold a short-term view to maximise any price change related savings. The potential of risk-sharing, where the NHS is able to be a partner in product development, should also be explored.

Scenario 2

In this scenario, manufacturers supply a range of licensed predefined doses which cover all doses over a predefined BSA range including dose reductions. This scenario depends on the acceptance and consensus on standardisation of chemotherapy doses using methodology such as dose banding.

Traditionally, there has also been limited consensus on prescribed doses following dose reduction from treatment toxicities, which has prevented full dependence on dose banded range of products.

These products would be either RTA or RTU, e.g. prefilled syringes, ready diluted bags or vials, and pharmacy preparation units would be responsible for manipulation and preparation of individual doses by addition to infusion bag, reconstitution and drawing into final container as per current practice.

Advantages of scenario 2:

1. Minimal in-process wastage, reduced manipulation within aseptic areas and more efficient use of existing facilities.
2. Improved responsiveness and reduced turn-around times for requests.
3. Reduced dosing error risks, particularly in terms of preparation and dose calculation.
4. In terms of patient safety this could mean unique vial sizes for each chemotherapy drug. This would reduce the risk of errors from 'picking errors' caused by similar corporate packaging and vial sizes, e.g. epirubicin and doxorubicin, both available in 10 mg and 50 mg vials.
5. Vials with the exact doses could be available with potentially reduced manufacturing costs (dependant on manufacturing processes).

Challenges to scenario 2 include:

1. Consensus and agreement of dosing strategies, dosing schedules, presentations and clinical management of chemotherapy toxicities.
2. Development and licensing costs—is the in-market price for drugs attractive enough for manufacturers to commit resource and time to license a wider range of presentations?
3. Changes in demand, either in terms of use of the drug or the dose, for the product over the lifetime of a 'batch' or of a licensed product.

Scenario 3

This scenario builds on scenario 2, with the added utilisation of smart pump technology and the use of RFID labelling. Vials, prefilled concentrated bags or prefilled syringes supplied by chemotherapy manufacturers, are dispensed to the clinical area directly after addition of an RFID label by pharmacy.

The RFID labels are read by the smart pump which then determines the reconstitution, dilution and/or volume to be infused for the specified patient. This technology facilitates near patient dilution and reconstitution of drugs using programmed settings in the smart pumps.

Smart pumps which allow independent control of multiple administration lines have recently been adopted at several centres in the UK. These are currently used for administration of chemotherapy including concentrated drug presentations, e.g. epirubicin syringes for IV bolus administration and use of independently controlled running infusions.

It could also be envisaged that closed docking systems [33], i.e. systems which do not exchange unfiltered air or contaminants with the adjacent environment, could facilitate the use of vials, concentrated infusion bags or concentrated syringes and dilution using the smart pump.

Advantages of scenario 3:

1. On-demand preparation of chemotherapy in near patient areas (with appropriate pharmacy controls to manage chemotherapy risks).
2. Use of RFID labelling allows greater safety, control and documentation of chemotherapy dispensing and administration process.
3. Minimal in-process wastage, reduced manipulation within aseptic areas and more efficient use of existing facilities.
4. No need for manufacturers to change existing presentations (though some new packs might still be needed to minimise waste of high-cost drugs).
5. Administer exact volumes removing the need for dose banding and overcoming a lack of consistent approach to such methodology.

Challenges to scenario 3 include:

1. Some products may not lend to manipulation by smart pump technology, e.g. drugs with complex reconstitution methodology or products currently supplied in containers which cannot be used by the smart pump—products in ampoules; viscous drugs, e.g. docetaxel and monoclonal antibodies.
2. In-process waste will still occur and some new packs might still be needed to minimise waste of high-cost drugs. Benefits of 'vial sharing' would not be possible.
3. Added risk if chemotherapy is prepared and administered without pharmacy checks and controls.

Conclusion

In reality no single scenario is able to provide the ideal solution for the challenges facing pharmacy chemotherapy services. A standardised dose-banding system would enable rationalisation and standardisation in chemotherapy preparation services and encourage suppliers to provide presentations reflecting chemotherapy dose bands.

A partnership with manufacturers is required to encourage development and uptake of standardised presentations and to enable the commercial viability of these products in practice.

Glossary

Batch preparation: practice of bulk preparing fixed doses of drug preparation in anticipation of a prescription.

Dose banding: a system where through agreement between prescribers and pharmacists, doses of cytotoxics, calculated on an individual patient basis, which are within defined ranges or bands, are approximated to standard doses (usually mid-point of the band). Maximum variation between the prescribed and standard dose is ≤ 5%. A limited range of prefilled syringes (hospital or industry source) is used to provide the standard dose.

Manufacturers' Specials Licences: licence to manufacture medicinal products granted by the Medicine and Healthcare Products Regulatory Authority to prepare specials. 'Specials' do not have a marketing authorisation or product licence, and do not need to have a qualified person to release the product.

Pharmacy technical services: branch of hospital pharmacy in the UK, involved in the dispensing, preparation and manufacture of drugs and doses not available to patients in a ready-to-use form.

Section 10 exemption: medicines prepared for a specific patient in accordance with a prescriber's instructions. This is usually a one-off dispensing of a compounded product against an individual prescription.

Special: an unlicensed relevant medicinal product placed on the market in order to meet the special needs of an individual patient.

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