

Guidance on Handling of Injectable Cytotoxic Drugs in Clinical Areas in NHS Hospitals in the UK

Edition 1

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Intended audience:

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

Nursing staff who handle cytotoxic chemotherapy (Oncology / Haematology plus other areas)
Pharmacy Aseptic Services Staff and Chief Pharmacists
Hospital senior management and Health and Safety / Risk Assessment / governance leads
Outsourced or in-house cleaning / portering service providers
NHS policy makers

In order to implement the contents of this document, it is recommended that a group consisting of the stakeholders named above performs a gap analysis to identify changes required. Change implementation should then follow the individual organisation's policies for medicines management as appropriate.

Overview / Scope

This document provides guidance on the handling of cytotoxic chemotherapy and its focus is on traditional small molecule chemotherapy although there are references to biological therapies including monoclonal antibodies which are being used in increasing numbers.

Many cytotoxic drugs are known to be mutagenic, carcinogenic and teratogenic due to their activity at the cellular level with the potential to cause damage to genetic material which can be an important part of their activity. Staff exposure to these agents therefore carries a degree of risk, as with other mutagenic, carcinogenic substances therefore exposures should be kept to a minimum. The principles described below apply to all environments and all staff handling cytotoxic drug but the document and its recommendations are aimed primarily at nursing staff handling these agents in clinical areas.

The recent Cochrane review of closed systems use for cytotoxic chemotherapy¹ concluded that there is currently no evidence to support or refute the routine use of closed-system drug transfer devices in addition to safe handling of infusional hazardous drugs, as there is no evidence of differences in exposure or financial benefits between CSTD plus safe handling versus safe handling alone (very low-quality evidence). None of the studies report health benefits.

However, the authors of this document feel that actions need to be taken in the short term to reduce exposure risks for nursing staff. It is hoped that a controlled study will be carried out in order to more fully assess the risks associated with cytotoxic chemotherapy, in the meantime the simple measures suggested within this document should be adopted in order to better control staff exposure to these agents.

Key recommendations for cytotoxic users

- 1) The practice of de-spiking “empty” bags of cytotoxic chemotherapy should be stopped as it provides unacceptable exposure risks for staff, other patients and visitors.
- 2) Ready-to-administer bags should either be accessed using spike free connections (needle free bags) which then remain connected for disposal or should be spiked with closed system devices (working over a tray) to allow safe disconnection (of the closed system device) following administration. Any connections which do not specifically require disconnection should remain in place.
- 3) Closed system caps should be added to syringes for IV use following removal of the storage cap immediately before connecting to the patient. (There is not currently a solution for intrathecal or sub-cutaneous injections).
- 4) Cytotoxic bladder instillations should always use closed system catheters.
- 5) PPE should be assessed and validated as suitable for use (i.e. offering protection with cytotoxic drugs) and should meet with local policies and guidelines, this should be available to all staff including cleaning staff.
- 6) Training in cytotoxic handling, including the immediate actions to be taken in the event of the spillage of cytotoxic drugs, dealing with small leaks and droplets of cytotoxic drugs and handling patient waste should be provided to all staff including cleaning, portering and waste management staff. This training should be regularly updated and should be specific to role.

Additional recommendations for suppliers of safe handling consumables and other parties

- 7) Devise manufacturers / suppliers should provide the required information in terms of integrity and product compatibility and stability to enable closed system syringe caps to be able to be added in aseptic services. Stability studies should be in compliance with NHS guidance¹³.
- 8) A research project to look at the impact of the use of closed systems in chemotherapy preparation in the UK needs to be undertaken to fully understand this area.
- 9) A national register of staff involved in handling cytotoxic drugs at both pharmacy and ward level should be produced and maintained in order to give a resource for future monitoring of exposure risks.

Background

In late 2016 the European Union released policy recommendations on preventing occupational exposure to cytotoxic and other hazardous drugs² which listed 11 recommendations for reducing / preventing exposure of staff to cytotoxic and other hazardous drugs. Recommendation 1 states 'in order to face an increasing occupational challenge, the EU and Member States should pay greater policy attention to the risk posed by the exposure of healthcare workers to chemical risks during activities such as the preparation and administration of cytotoxic drugs, given the consequences to healthcare workers health'.

Within the UK practically all cytotoxic chemotherapy is prepared in either NHS or commercial aseptic compounding units either under the supervision of an Accountable Pharmacist or under a MHRA Specials Licence. Pharmaceutical isolators are used in a vast majority of centres (normally under negative pressure) and this technology goes some way towards controlling the exposure of staff preparing chemotherapy. Following implementation of the Sharps regulations³ needle free devices are now advocated for reconstitution and drawing up of cytotoxic drugs. The use of Closed System Transfer Devices (CSTDs) within aseptic compounding service is not currently standard practice and due to the cost implications of their introduction, further evidence is required to establish if their use would decrease contamination levels on prepared items leaving the work zone.

In some units all items prepared are wiped with alcohol wipes ahead of removal from the work zone, this is, however, not always the case and further work is required to assess the impact of this on contamination levels of items being removed from isolators. This evidence is likely to come to light in analysis of the data from surface monitoring of NHS pharmacy aseptic units required by the 5th Edition of the Quality Assurance of Aseptic Preparation Services⁴.

There is published evidence that engagement with manufacturers of licensed starting material vials has resulted in substantial reductions in the external contamination levels on vials leaving filling lines and this has transferred to reduced levels of cytotoxic contamination in aseptic facilities over the past 15 years⁵. For example, vials are now routinely washed following filling in the factory and most are now coated in a plastic sleeve ahead of supply.

The area of cytotoxic drug administration and the exposure of nursing staff to these agents has not received the same level of oversight to date and there are no nationally agreed standards available in this area. It is this which is the main scope of this document which aims to remove unsafe practices and to ensure better control of exposure for nursing staff and also ancillary staff in chemotherapy clinics and areas.

The risk areas for nursing staff are generally focused on connection and disconnection of cytotoxic chemotherapy infusions in bags and also connection and disconnection of doses in syringes. The use of dose banding has increased significantly the number of syringes connected and disconnected as part of standard treatment as combinations of syringes are used to make up each patient dose, sometimes across a range of drugs. The spiking of IV bags ahead of infusion has

been shown to cause cytotoxic contamination in 25% of cases, however, the removal of spikes from completed infusions (de-spiking) has been shown to cause contamination in 100% of cases⁶, furthermore this leaves a leaking bag to transfer to the cytotoxic waste bin which will leak out into the bin and risk causing further exposure. The practice of de-spiking bags is totally unnecessary with the technology available and the practice must not be allowed to continue (see below for further advice).

There is concern among nursing staff as to the adverse effects that they may be suffering as a result of administering chemotherapy⁷, however, the evidence for longer term issues such as cancer takes many years to come to light. Many papers published reporting increases in carcinogenic, mutagenic and teratogenic effects from handling cytotoxic agents cover staff who were working to past standards of practice^{8,9,10}, and with cytotoxic agents that were used in those days. Staff should be reassured that greatest risk comes from reconstitution activity and as they receive all items as ready-to-administer the medicines themselves are presenting a minimized risk though this cannot be said to be negligible without further evidence. However, there is increasing usage of cytotoxic chemotherapy in oncology and haematology units as well as in other areas and hence it is vital that measures are taken to minimize staff exposure to these agents in order to manage the risks.

There are also increases in the use of monoclonal antibodies and other biological therapies and these drugs have not been used for a long enough period for staff exposure risks to be totally understood. There is a separate standards document on handling of monoclonal antibodies¹¹. Due to the complexity of these molecules there are more likely to be concerns with compatibility with various close system devices and assurances need to be sought from manufacturers of both drugs and devices as to this issue.

Recommendations for administration of cytotoxic chemotherapy

Personal Protective Equipment (PPE)

It is vitally important that suitable PPE is used whenever cytotoxic drugs are handled. Suitable cytotoxic resistant nitrile gloves should be donned at all times when handling primary containers of cytotoxic infusions. When spiking bags, PPE including suitable gloves, protective sleeves, polythene aprons and eye protection should be worn. When connecting / disconnecting chemotherapy to patient administration sets at the bedside then suitable gloves, polythene aprons and eye protection should be used and work should be over a clean tray. PPE should also be used for disposing of waste etc. It is the responsibility of unit management to ensure that the manufacturers of PPE are consulted in order to obtain assurance of protection against the range of cytotoxic chemotherapy being used. For gloves this should include assessment of the breakthrough times to indicate maximum periods of use.

Suitable PPE should also be used by domestic staff providing cleaning services to oncology and haematology units or other ward and clinic areas where cytotoxic drugs are handled. Equipment used for cleaning these areas should be designated.

Training of nursing staff

Training in the risks and control measures for handling cytotoxic drugs including correct use of the suitable PPE and techniques must be provided to all nursing staff working with chemotherapy agents. The efficiency of this training should be assessed using workplace observations and update training should be provided at regular intervals in accordance with local policies, as a minimum annually.

Recommendations for IV infusions in infusion bags

The main area of risk for nursing staff with IV infusion bags is in the connection and disconnection of cytotoxic chemotherapy. There is a risk of exposure during spiking of IV bags, and it has been reported that contamination occurs on 25% of cases, however, the practice of de-spiking bags always results in contamination (i.e. 100% of the time)⁶ and furthermore leaves a leaking bag for disposal. The practice of de-spiking bags of chemotherapy should be stopped as it presents unacceptable and unnecessary risk to nursing staff. Under Health and Safety legislation it is the responsibility of employer to carry out a risk assessment and mitigate the risk as far as is practicably possible.

The authors suggest that one of the below two solutions are adopted by all cytotoxic chemotherapy units to prevent the need to de-spike bags and to allow for safe handling and disposal of cytotoxic infusions.

Option 1

Aseptic services units should provide the chemotherapy in a bag with a needle free access port. The port is used for addition of the drugs to the bags and should then be covered with a removable cap and sealed for tamper evidence (ideally with a seal over the cap although it may be acceptable to provide the capped bag heat sealed in polythene). For administration the cap should be removed, the port swabbed with an alcohol-impregnated wipe and then connected to a male port on a safe system administration set. This can then be connected to the giving set through a 'Christmas tree' connector which is connected to the flush bag. Each infusion is connected to a separate connector on the Christmas tree and is left connected following completion of the infusion with the line being clamped off.

Once all infusions have been completed and the final line flush run through, the whole set can be removed and disposed of.

Option 2

The product is supplied to the administration area in a traditional infusion bag. The bag then needs to be spiked with a closed system device, using the standard administration port working over a clean tray to contain any spillage. This device is then connected to a closed system transfer device giving set which ensures that a closed system is maintained on connection and removal. Following flushing of the line, each bag of cytotoxic chemotherapy is then removed from the giving set and replaced with the next bag; the used bag can

be discarded with the spike still in place. Alternatively a 'Christmas tree' set could be used with this scenario removing the need for any disconnections.

Note that bags cannot be supplied from aseptic services with a spike already present due to concerns about the integrity of the bag/device connection during storage, transport and ongoing handling³.

Bag fill volumes

In terms of good aseptic technique then the number of aseptic manipulations in a process should be minimized, this means that aseptic units are discouraged from removing volumes from bags ahead of addition of drug solutions, this is part of the national specifications linked to the standardization of cytotoxic doses¹². However, overfilled bags do present an increased risk particularly if the bag has to be spiked, due to the excessive internal pressure, and hence safe maximum addition volumes should be agreed between nursing staff and the pharmacy aseptic service.

Recommendations for IV infusions in Syringes

Current position

Pre-filled syringes are sealed with solid plastic syringe caps. This combination of syringe and cap has been subjected to extensive integrity testing over many years to prove that product sterility is maintained. Similar data is not currently available for closed system devices. There is a risk of cytotoxic contamination being released on removal of the cap, connection of the syringe to the giving set and disconnection of the syringe following administration. In order to minimize these risks it is recommended that closed system syringe caps are added to each syringe when the original cap is first removed. The original cap can then be discarded straight away in a suitable cytotoxic disposal container. In this way the risks on connection and disconnection of the syringes from the giving set is removed and after use the syringe can be disposed of with the closed system cap still in place. It should be noted that closed systems may not be compatible with all types of pump used for chemotherapy administration. Compatibility should be checked for all pump systems in-use.

Consideration needs to be given to significance of the 'dead space' within the closed system cap, however, for most volumes given by syringe this will be insignificant and with careful handing it may be possible to remove the air from the dead space into the main body of the syringe.

Recommendations for future work

Suppliers of closed system transfer syringe caps are encouraged to invest in testing to show the integrity of their products are suitable for use to seal pre-filled syringes intended for storage prior to use. Test should evaluate the range of syringes being used for chemotherapy administration, together with drug compatibility / stability information to support their use across the range of products. If this work is available

and robust and the results are made widely available, aseptic services both within the NHS and the commercial sector would be able to supply products with the closed system cap already applied. It is likely that such systems will need to be supplied with an additional protective cap to allow long term storage (i.e. a dust cap that protects the valve device but does not open the valve). Note that the valves themselves cannot be opened without connection to a female connector and hence they could be considered as tamper resistant. Hence, presenting this container/device combination in a heat-sealed plastic overwrap should be sufficient tamper-evidence.

Elastomeric infusors

Elastomeric infusors are used for delivery of cytotoxic agents over extended periods (normally 24 hours to seven days). Due to the nature of these devices it is not currently possible to attach closed system devices and hence they will still need to be connected and disconnected with a risk of cytotoxic exposure for staff. Suitable PPE (see above) should be worn for these tasks. The suppliers of elastomeric infusors are encouraged to consider this risk and whether closed systems can be developed to allow safe connection and disconnection of these infusors without impacting on infusion rates and drug delivery.

Sub-cutaneous injections

These are necessarily given using a needle and also tend to be small volumes, hence closed system devices are not suitable for injections given by this route. Appropriate PPE must be used for administration of subcutaneous cytotoxic injections.

It is advised that for monoclonal antibody injections being drawn up in the ward environment closed system transfer devices are used where compatibility data allows, and appropriate PPE including eye protection is worn; refer to Guidance on the safe handling of Monoclonal Antibody (mAb) products¹¹ for further information.

Intrathecal Injections

These injections are provided in purpose designed intrathecal syringes to minimise any risk of inappropriate route errors, and are necessarily given using a needle and also tend to be small volumes, hence closed system devices are not currently available or suitable for injections given by this route.

Bladder installations

This route represents quite a high risk of cytotoxic contamination during installation and closed systems should be used for administration. Mitomycin bladder installation is often prepared using closed systems and connected via closed systems to the catheter. Other products are supplied in pre-filled syringes and need to be connected to catheters directly.

Patient urine will be heavily contaminated with cytotoxic drugs following these procedures and this is likely to cause significant contamination in toilets.; it is

particularly important that specific toilets should be assigned and restricted for the use of these patients and that domestic staff are trained in safe practice.(see below).

Waste Disposal

Cytotoxic-contaminated waste has to be disposed of safely following use, and waste products should be placed immediately in a suitable labelled cytotoxic waste bin or disposal bag (purple waste stream). Where giving set and bag combination are disposed of intact and there should therefore be no sharps, it is easier to use an appropriate waste sack or bag rather than trying to force the units into a burn bin through the narrow opening. Double bagging may be advisable depending on the quality of the waste sacks and local policy. There are also airtight waste disposal systems available that are specifically designed for disposal of cytotoxic, infectious and clinical hazardous waste. Use of these would further minimize the risk of exposure.

Cleaning of chemotherapy clinical areas

Chemotherapy clinics and wards are still likely to have some level of cytotoxic contamination from routine patient and staff contact small amounts of leakage etc. It is therefore vital that domestic staff are aware of the issue and the areas which may be contaminated and take suitable precautions including using suitable PPE when cleaning. It is also important that agents used are suitable for removing cytotoxic residues and include sufficient detergent activity. Ideally disposable mop heads and wipes should be used for these areas, these should be disposed of as cytotoxic contaminated waste. Specific programmes should ensure that all domestic staff have been trained to a suitable level for the tasks carried out. Where cleaning services are contracted out it is important that the specifics of cleaning chemotherapy areas are included in contracts and Standard Operating Procedures.

Trays over which bags are spiked may also become contaminated. They must be cleaned using validated procedures and suitable agents including neutral detergent to ensure residue removal after each use. Alternatively disposable trays should be used.

Staff should be aware that contamination can quickly and easily be spread from gloves used to handle chemotherapy, particularly for spiking bags, and for handling patients and patient waste. It is important that gloves which may have become contaminated are removed or changed before touching other areas which would not be expected to be contaminated with cytotoxic drugs such as computer keyboards, telephones etc.

An approach of specifying and labelling areas of the chemotherapy clinic as 'gloves' for those areas which may be contaminated and 'no gloves' for areas which are not expected to be contaminated, can be useful to promote staff discipline and best practice.

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