National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Guidance:

Pharmacy bench top preparation of monoclonal antibodies (mAbs) used in the treatment of cancer

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Contents

Glossary

Aseptic Compounding Unit (ACU)	An ACU is a specialised suite of graded rooms with engineering controls such as HEPA filtration that contains specialised equipment such as isolators
Benchtop preparation	The preparation of parenteral SACT outside of a physical separator device for immediate use.
Closed system transfer device (CSTD)	A CSTD is a drug transfer device that transfers a drug from one reservoir to another while limiting the potential for exposure by mechanically prohibiting the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapour concentrations outside the system.
Physical Separator Device	This includes an isolator in an ACU or other devices where there is a barrier between the operator and product.
Personal Protective Equipment (PPE)	PPE is equipment that gives an additional layer of protection to the operator/user against health or safety risks in the workplace. Examples of PPE include gown, gloves, eye goggles and masks.
Systemic Anti-Cancer Therapy (SACT)	SACT involves systemic treatment for cancer; involving parenteral and oral anti-cancer therapies, including but not limited to chemotherapy, targeted therapies and immunotherapies

1 Introduction

Systemic Anti-Cancer Therapy (SACT) is one of the main cancer treatment options together with surgery and radiation. The continuity of supply of parenteral SACT for the treatment of patients has been a key consideration for the HSE, the DoH, HIQA and patient advocacy groups over the last number of years. This has been of particular concern during Brexit and the global Covid-19 situation.

There are 26 public hospitals providing SACT cancer services. The centralisation of SACT preparation in pharmacy departments followed from the publication of the Department of Health's "Guidelines for the safe administration of cytotoxic medical preparations in the treatment of patients with cancer" and the National Cancer Strategy of 1996 and 2006.

The development of pharmacy SACT services varied across the 26 hospitals resulting in different models of preparation and provision of SACT including local compounding in a controlled environment such as an Aseptic Compounding Unit (ACU) or stand-alone cabinet, on bench top or outsourced.

There is a capacity issue within pharmacy department SACT compounding in addition to a growing demand for SACT treatment.

This document focuses on the pharmacy bench top preparation of monoclonal antibodies to support this process in hospitals without a dedicated ACU or where capacity in the ACU is insufficient. It provides guidance for individual organisations to assess the relevant factors and suggests a range of risk minimisation and control measures for consideration in providing a bench top service compounding monoclonal antibodies (mAbs).

2 Scope

This document focuses on bench top preparation of mAbs, used in the treatment of cancer, by hospital pharmacy department staff, excluding:

- Conjugated antibody-drug complexes
- Radiolabelled antibodies

It considers how hospital pharmacy departments, with and without ACUs, may facilitate "bench top" preparation of mAbs. The principles of this document may be applicable to the preparation of mAbs by staff other than Pharmacy outside of a physical separator device.

3 Methodology

This guidance document has been informed by published literature and international practice. The document was developed and agreed by the NCCP in consultation with the Parenteral SACT Resilience Group.

4 Centralised preparation of Systemic Anti-Cancer Therapy

The 1996 DoH published document "Guidelines for the safe administration of cytotoxic medical preparations in the treatment of patients with cancer" advised that all cytotoxic drugs should be prepared by trained pharmacy personnel in a contained environment (e.g. isolator units, bubble units or laminar airflow cabinets) to improve patient safety in addition to minimising risk of exposure (1).

These guidelines prompted the move to centralised pharmacy department aseptic compounding of SACT. These services initially used laminar air flow cabinets, progressed to stand alone isolators and eventually to Aseptic Compounding Units (ACUs) (dedicated clean rooms) where service demands required extension of expiry dates to ensure service continuity and efficient service operation. Some hospitals put no centralised services in place due to low volume demands which were catered for through outsourcing.

As a result there is a mixture of aseptic compounding services in the 26 public hospitals providing SACT cancer services. These include:

1. Hospitals with ACUs allowing for advance preparation of SACT as they have the facility to extend the expiry dates of the compounded products from a microbiological perspective.
2. Hospitals with stand-alone isolators - preparing product for immediate use
3. Hospitals completely dependent on outsourcing of compounded SACT

5 Hospital compounding capacity

The demand for SACT services is driven by the number of patients diagnosed with cancer and of these the number who will require SACT. The 2019 National Cancer Registry report estimates that the number of patients receiving SACT for the treatment of their cancer will increase by 58-81% (average of 70%) between 2015 and 2045 (2). This is reflected in the current service where many pharmacy department aseptic compounding services are operating at full capacity and are required to outsource to third parties which may result in an increased cost.

The NCCP established the Parenteral SACT Resilience group in 2019 with the aim of optimising resilience in the supply of SACT in Ireland. As outlined in the "Best Use of SACT Aseptic Compounding Capacity" agreed by that group, there is a finite amount of aseptic compounding capacity nationally**.** Hospitals are responsible for ensuring that adequate contingency planning is in place locally to ensure patient safety and continuity of care in the event that any major supplier's service is suspended or severely curtailed for any reason.

All hospital pharmacy departments are considering how best to manage the continued challenges to services for the safe supply of parenteral SACT in the immediate, medium and long term.

6 mAb preparation – challenges and enablers

mAbs used in the treatment of cancer are mainly prepared in a hospital pharmacy department or outsourced to third party providers. The drivers for this are:

1. One point of dispensing for the patient's treatment i.e. parenteral cytotoxics and mAbs for SACT being checked and dispensed through the same process
2. Local risk assessment which considers clinical (medication error) and operational (complexity) factors (3, 4, 5)
3. Value for money – vial sharing and reduction in waste. mAbs tend to be high cost treatments best suited to a "just in time" preparation to avoid wastage.

6.1 Stability

There has been a significant increase in the number of mAbs used in the treatment of cancer. Many of the newer mAbs have short expiry dates once compounded which restricts their use to hospitals who prepare mAbs locally. This may limit the treatment options which are available for patients in hospitals without a local aseptic compounding service.

6.2 Complexity of preparation

There are varying complexities associated with mAb preparation. The majority are associated with a complexity band level two (6) which would support a decision to bench top prepare these products. A key factor in this is that as many of the newer mAbs are presented in sizes aligned to their flat dose; there is a reduced need for manipulation and individualised dose calculation.

6.3 mAbs – Operator Protection

There is existing variation in the handling of mAbs across hospitals and disciplines where mAbs may be compounded by nursing staff at ward level or by pharmacy staff in the hospital pharmacy/compounding unit. The mechanism of action of mAbs is associated with cell-mediated cytotoxicity rather than the direct cytotoxicity of traditional anticancer agents. In view of this, the occupational exposure risk characteristics are considered to be different to cytotoxic agents i.e. teratogenicity, mutagenicity or carcinogenicity (3, 7).

The Australian Guidelines for the Safe Handling of mAbs (2014) considered the potential for occupational exposure with mAbs (8). They found that while from an occupational health and safety perspective it was prudent for mAbs to be managed with greater handling precautions than other non-hazardous injectable medications, mAbs did not warrant full cytotoxic precautions. The group considered that although toxicity profiles may vary, all currently available mAbs have a low risk of internalisation at occupational exposure levels.

The National Institute for Occupational Safety and Health (NIOSH) adopted a set of criteria to identify the characteristics of a hazardous drug. mAbs have limited data associated with many of these characteristics. Indeed, as they are proteins in nature, mAbs are not required to be evaluated for carcinogenicity or genotoxicity, even if their therapeutic effects are directly mediated by antibody binding to target antigens. The 2016 NIOSH[1] list of antineoplastic and other hazardous drugs in healthcare settings do not include mAbs as hazardous except those mAbs conjugated to cytotoxic agents or radio-isotopes (9).

There is little formal data available on the potential exposure risk to staff handling mAbs as it is not required for licensing purposes. Safety Data Sheets (SDS) are available but tend to be specified towards industrial processing of raw materials rather than the clinical setting.

7 Considerations for bench top preparation in pharmacy

Some hospitals have an ACU and others utilise stand-alone cabinets such as laminar air flow cabinets, Isolators or biological safety cabinets. The preparation of SACT in a physical separator device within an ACU or a stand-alone cabinet provides protection to the operator from exposure to hazardous drugs, may

[1] To note the 2016 list includes pertuzumab listing a Black Box warning on embryo-fetal death and birth defects; FDA Pregnancy Category D. However the draft 2020 NIOSH list states "NIOSH reviewed data concerning the developmental effects related to pertuzumab treatment and has determined that it is unlikely that pertuzumab poses a reproductive threat to workers in healthcare settings and is no longer considered a hazardous drug by NIOSH."

allow expiry times of prepared products to be extended and reduces the risk of contamination of the prepared product.

The following points should be discussed and considered in a local context when evaluating whether mAbs would be prepared outside an ACU environment and if so which mAbs are appropriate:

1. Risk Assessment/Safety
2. Staffing and Training
3. Equipment/facilities
4. Range of treatment options that the hospital can provide
5. Value for money

7.1 Risk assessment/Safety

There is no known or potential mechanism of internalisation through dermal contact due to their high molecular weight, the most likely form of contact is when cleaning or disposing of contaminated waste.

A local risk assessment should be undertaken, using the HSE Risk Assessment Tool[2], on each product to determine whether it is appropriate for bench top preparation[3]. Additional risk assessment tools may also be considered during the risk assessment process (8, 10, 11, 12). Each risk assessment should consider the following along with any additional local considerations:

- likelihood of exposure
- complexity of manipulation
- staff experience and staffing levels

A sample risk assessment is included in Appendix 1 of this document.

[2] HSE Risk Assessment Tool https://www.hse.ie/eng/about/qavd/riskmanagement/risk-assessment-tool.pdf

[3] Risk assessment may be further informed by risk assessment tools such as Australian Consensus Guidelines for the safe handling of monoclonal antibodies by Western and Central Melbourne Integrated Cancer Service (WCMICS)

7.1.1 Personal Protective Equipment (PPE)

There is limited evidence of toxicity resulting from low-grade occupational exposure to mAbs (12). PPE should be considered for use when preparing mAbs on a bench top to minimise any potential risk of contamination and infection. This may include:

- Gloves including correct handwashing technique
- Aprons
- Eye protection
- Masks

7.2 Staffing and Training

1. There should be an appropriate number of staff[4] available (13)
2. A local training programme should be in place. This should detail all aspects of staff training and safety including but not limited to:
    - Aseptic Non Touch Technique (ANTT) SOP
    - List of mAbs eligible for preparation and identified in relevant SOPs
    - Validation of staff training and technique
    - Safe handling precautions to minimise risk of exposure(14)
    - Cleaning – SOPs and validation
    - Audit of all of processes involved
    - Incident management e.g. management of staff exposures, spillage etc.

7.3 Equipment/facilities required

7.3.1 Preparation area

Engineering controls are not essential for bench top mAb preparation

[4] Refer to the Hospital Pharmacy Cancer Service Workforce Planning Framework

- mAbs may be prepared on a bench top as are many other medications including those used in cancer and non-cancer indications.

The principles of aseptic preparation technique apply when preparing any parenteral medication. The following should be considered to ensure the facilities available for bench top preparation provide the optimal environment for safe preparation:

- The area chosen for preparation should be:
    - Dedicated and free of interruptions
    - Well ventilated, clean, free from clutter and easy to maintain
- Where stand-alone cabinets are utilised:
    - There should be Standard Operating Procedures in place for maintenance and cleaning
    - There should be sufficient space around the cabinet to ensure airflow is not adversely affected and product/operator protection is negated

7.3.2 Consumables – Closed system transfer devices (CSTDs)

CSTDs, as a needle free or needle safe system, award an additional layer of protection to the product and operator during preparation. However, it is important to understand the characteristics, benefits and risks associated with different CSTDs when considering the use of this technology:

a) The practice of safe handling and aseptic no-touch technique is key to the prevention of product contamination

b) NIOSH define CSTDs as "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapour concentrations outside the system"

c) CSTDs currently consist of two design concepts – physical barrier or air cleaning technology to prevent escape of vapour, each have advantages and disadvantages depending on design and functionality

d) They allow preparation of drugs without needles, or are needle safe, therefore eliminate or reduce needle-stick injury risk

e) There are technical differences between brands of CSTDs therefore the assessment of each system is required in terms of function, design, cost, compatibility with vials and aseptic integrity

f) A written SOP on the use of the CSTD system is required

7.3.3 Waste management

mAbs do not have direct cytotoxic activity and are not classified as cytotoxics, therefore they can be managed as non-cytotoxic waste. This should be reflected in the relevant waste management SOPs.

7.3.4 Range of treatment options that the hospital can provide

There are a number of hospitals completely dependent on outsourcing of compounded SACT. The limited expiry of some compounded mAbs precludes supply from out-sourcing companies therefore this limits the range of treatment options that the hospital can provide. Local bench top preparation of mAbs for immediate use may allow additional treatment options to be provided in hospitals closer to patients' homes.

7.4 Value for money

Bench top preparation of mAbs just in time/for immediate use in hospital pharmacy departments may result in cost savings through a number of means including;

- Reduction in drug wastage as preparation should not occur until the patient is confirmed fit for treatment.
- Local preparation may provide better value than that of external suppliers.

8 Conclusion

Pharmacy bench top preparation of mAbs may improve capacity in hospitals with ACUs or utilising stand-alone cabinets. In hospitals with no local SACT compounding, it may represent an opportunity to increase the range of treatment options available, facilitating cost effective treatment of patients closer to home.

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Appendix 1. Sample Risk Assessment Template

Sample Risk Assessment for Bench Top Preparation of a Monoclonal Antibody

The below is a sample risk assessment for the bench-top preparation of a monoclonal antibody (no particular drug has been used in this case rather generic considerations have been included).

There are several methods that can be employed when completing a risk assessment which may be stipulated by your individual institution. The below method considers the risk associated with the process, the consequences of that risk and any actions, controls or mitigations employed or available. The risk is then rated according to the HSE risk matrix and local acceptability determined.

The risks and mitigations used in this sample risk assessment are guided by this document. A completed risk assessment should also include reference to the relevant product information (SmPC, SDS), other relevant references (for example the Australian Consensus Guidance document) and local considerations (including staffing, skill mix, equipment, engineering controls, location).

Risk	Consequence	Actions/Controls/Mitigations	Grade		
			Consequence	Likelihood	Rating
Medication error due to incorrect preparation	Patient may receive incorrect dose of medication leading to either suboptimal or toxic response	SOP details checking procedures undertaken during preparation and release of the product Staff involved in preparation have received training in accordance with the relevant SOPs The medication is available in liquid form and requires no reconstitution step	**This is graded in accordance with the HSE Risk Matrix**		
			Major (4)	*Rare/Remote (1)*	*Low Risk (4) - Accept*
Acceptability – The risk is considered acceptable based on the actions and controls in place when preparing this monoclonal antibody by trained staff in the designated preparation area in the pharmacy					

Risk	Consequence	Actions/Controls/Mitigations	Grade

			Consequence	Likelihood	Rating
Physicochemical or Microbiological Instability of prepared product	Patient may receive insufficient dose or toxic metabolites. Patient may develop infection due to microbiological contamination during preparation	Medications prepared immediately prior to administration Monoclonal antibodies are prepared in a cleaned, designated area Staff involved in preparation have received training and have been validated in aseptic techniques and safe handling Staff involved in preparation wear sterile gloves during preparation following validated hand hygiene procedures The SPC for the product indicates physicochemical stability sufficient for the duration of preparation and administration	**This is graded in accordance with the HSE Risk Matrix**		
			Major (4)	*Rare/Remote (1)*	*Low Risk (4) - Accept*
Acceptability – The risk is considered acceptable based on the actions and controls in place when preparing this monoclonal antibody by trained staff in the designated preparation area in the pharmacy					

Risk	Consequence	Actions/Controls/Mitigations	Grade		
			Consequence	Likelihood	Rating
Risk of teratogenicity and/or carcinogenicity due to occupation exposure – medication has potential risk of teratogenicity and carcinogenicity at therapeutic doses in animal models (SPC)	Staff preparing medication suffer adverse effects due to occupational exposure to the medication	Effects at long-term low-dose exposure levels are unquantified and indeterminate Internal exposure risk is moderate via the inhalation and mucosal route, low via the oral route and unlikely possible via the dermal route in the absence of additional controls A closed system transfer device will be utilised during preparation which will reduce potential occupational exposure. All staff involved in preparation have been trained on use of this CSTD Staff involved in the preparation of this medication will wear non-penetrable gown, nitrile gloves, protective mask and eye wear to further limit exposure	**This is graded in accordance with the HSE Risk Matrix**		
			Major (4)	*Rare/Remote (1)*	*Low Risk (4) - Accept*
Acceptability – The risk is considered acceptable based on the low risk of internalisation of the medication coupled with the use of PPE, CSTD and safe handling precautions.					