GUIDANCE ON THE SAFE HANDLING OF MONOCLONAL ANTIBODY (mAb) PRODUCTS

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ACKNOWLEDGEMENTS

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Introduction

Occupational health and safety (OHS) exposure risks associated with traditional cytotoxic drugs are well established. However there is little information regarding the OHS exposure risks of monoclonal antibodies (mAbs). Hence these are often based on theoretical risks associated with the modes of action of the mAb, the risk of production of antibodies against the agent if future therapeutic treatment is needed or reactions due to the proteinaceous nature of the mAb.

mAbs either do not fulfil hazardous drugs criteria or lack sufficient agent-specific information to assign an appropriate hazard classification.

Industry level standards for correct handling and exposure risk associated with mAbs are aimed at large scale manufacture rather than reconstitution of patient specific doses from licensed products.

Operational and clinical issues (e.g. vial-sharing, preparation complexity and medication error risk) also influence how mAbs are handled. This often results in considerable site to site variability with the application of stricter standards associated with cytotoxic drugs in some settings and the limited use of safety precautions in other settings. It was this variation in practice which underlined the need for an evidence-based guideline for handling mAbs that was suited to all those providing care to NHS patients.

This guideline does not provide prescriptive recommendations for the preparation and handling of each specific mAb in every healthcare organisation due to the many influencing clinical and operational factors unique to operations in each organisation. Rather, the guideline provides a mechanism and guidance for individual organisations to assess these factors in their own facilities and suggests a range of suitable risk minimisation and control measures that may need to be considered.

It should be noted that this guidance is not intended to apply to antibody drug conjugates (ADCs),such as Kadcyla which due to the nature of the conjugated drug substance if unbound, should always be regarded as high risk and handled as cytotoxics within a Pharmacy aseptic unit. Similarly, radiolabelled mAbs would be considered to be outside the scope of this guidance and should be handled in nuclear medicine / radiopharmacy facilities.

Whether mAbs are prepared in the Pharmacy Aseptic Unit or elsewhere in the healthcare system, it must be remembered that medicines optimisation principles give the Chief Pharmacist the overall responsibility to ensure the safe and effective use of medicines within the organisation. Therefore, wherever in the organisation the preparation takes place, there must be sufficient input from suitably trained and experienced Pharmacy staff to ensure suitable environments and techniques for mAb handling. Some of the terminology in this document is pharmaceutical and may require pharmacy expertise to ensure that it is accurately translated into practice where mAbs are prepared outside of pharmacy

Risk Assessment

Broadly speaking, risks associated with handling of mAbs can be considered in 2 categories.

1. Risks of exposure to the mAb for staff handling the product due to the nature of or mode of action of the agent.

2. Risks to patient receiving the mAb due to the potential for errors or contamination during the preparation of the product.

When both of these factors have been assessed, a combined overall risk assessment score for the product can be allocated and from this suitable methods of preparation and risk mitigation measures implemented.

It is likely that the risks of staff exposure will be much greater during the preparation of mAb products, especially where there is a reconstitution step, than in the administration of a ready to administer solution made in pharmacy or bought in and so risk mitigation controls will be different depending on the activity being completed by different staff members.

Risks associated with the mAb being handled

This requires an expert assessment of the nature of the product being handled based on both COSHH ([1]) and pharmacological data combined with knowledge of potential risks of exposure.

Factors that should be considered at this stage should include:

1. Internal Exposure Risk via
- Dermal absorption
- Inhalation absorption
- Mucosal absorption
- Oral Absorption

2. Toxicity
- Cytotoxicity
- Carcinogenicity
- Genotoxicity or Mutagenicity
- Teratogenicity or other developmental toxicity
- Organ toxicity at low doses
- Immunogenicity

Based on the expert assessment of the above factors, each mAb should then be assigned a chemical hazard rating of Low, Medium or High.

Risks associated with the preparation process for each mAb

NPSA Alert 20 ([2]) established a widely accepted risk assessment methodology for injectable medicines within the UK and this approach has been widely used in all Trusts where injectable medicines are prepared.

All mAb preparations should be assessed using the NPSA 20 methodology and the product assessed again as a Low, Medium or High preparation process risk. Note that the risk may be different for different applications. eg preparation of Trastuzumab IV infusion as compared to use for the SC route.

Determination of Overall Risk Assessment profile

The outcomes of the handling and preparation risk assessments should be combined to create an overall risk assessment profile for the mAb concerned. These can be defined as:

High Risk: If both handling and preparation risk assessments are high or the handling risk assessment alone is high. For these products only preparation in a pharmacy aseptic unit is possible.

Medium Risk: If the handling risk assessment is medium or the preparation risk assessment medium or high. Suitable risk mitigation controls must be put in place as highlighted later in this document.

Low Risk: If both handling and preparation risk assessments are low. Product may be prepared in clinical areas with no further controls required apart from standard ward based aseptic technique.

Preparation in Pharmacy Aseptic units For High Risk mAbs (including radiolabelled mAbs)

mAbs may be manipulated in existing aseptic facilities, provided that adequate segregation from other products is achieved by the normal levels of process control expected within pharmacy aseptic units and the application of standard validated cleaning procedures.

The additional precaution of a final decontamination wipe of the final container should be applied to remove any trace external residues to reduce to a minimum any unnecessary exposure risks.

Ideally these products should be handled on a campaign (time separation) basis, but it is accepted that due to workload pressures this will not always be realistic. However, complete segregation and competent cleaning of surfaces should be routine practice between all products of a potentially hazardous nature.

Accidental spillage: Wear appropriate protective clothing, ie gloves, mask, apron. Wash and dilute the site of any spillage thoroughly with water and detergent, mopping up with absorbent materials and disposing of waste as a biohazard. Even within Pharmacy, extra risk control measures will be needed for ADCs. For example when dealing with spillages, use of agents that may denature the conjugate must be avoided as the hazards associated with the unbound drug substance will be much greater than the conjugate.

Risk Mitigation Strategies for Medium Risk mAbs

Preparation in Pharmacy Aseptic Units

If the facilities and capacity exist to do so the decision may be made that the risk can be best controlled by bringing the preparation of these products into the pharmacy aseptic unit. The conditions outlined above would apply.

This workload must be adequately resourced and within the capacity plan of the aseptic unit. Consideration must also be given to potential cost savings that may be achieved by using campaign preparation in the aseptic unit to enable vial sharing.

Outsourcing of Compounding to a Third Party provider

This arrangement must be managed by pharmacy and covered by relevant Technical Agreements and Service Level Agreements. It can also be an option for High risk products instead of preparing them within an in-house aseptic unit.

There must be systems in place for supplier assurance (including access to a relevant quality audit) and adequate resources within pharmacy to manage the outsourcing process, including product receipt, assessment and supply together with ongoing monitoring of the Technical Agreement and Service Level Agreement.

There should be agreed product specifications in place and these must also consider and evaluate the validity of any extended shelf life allocated. Any extended shelf life carries a level of risk and this is especially true with mAbs. Assessment must not only consider length of shelf life offered, but the validity, relevance and applicability of the data used to support this. This must be in compliance with the published NHS Pharmaceutical R&D Group guidance on this subject (ref to add).

Consideration must also be given to potential cost savings made by campaign working and vial sharing by the third party supplier.

Preparation in Clinical areas with appropriate levels of control to protect operators (also to include preparation for administration in the patient's home)

Personal Protective Equipment (PPE)

Staff preparing mAbs in clinical areas should have access to and use a range of appropriate PPE. This should include:

- Gowns
- Gloves
- Protective Eyewear
- Masks and Respirator masks

Standard surgical type masks will offer limited protection from aerosol droplets generated in the preparation process. Consideration should also be given to the use of a respirator mask. To help ensure adequate staff protection, all respirators provided for use at work should be CE marked to show that the design has been tested to a recognised standard. They must also be marked with that standard, which for disposable respirators is EN 149: 2001 [(3)]. Additional markings, such as FFP1, FFP2 or FFP3, indicate the protection level that can be attained if the respirator is a good fit and used correctly. The higher the number, the better the protection. FFP1, FFP2 and FFP3 respirators can reduce the amount of particles inhaled by factors of 4, 10 and 20 respectively.

Closed System Reconstitution Devices (CSRDs)

CSRDs are not seen as essential for use in the preparation of mAb doses; however they do provide an additional level of safety both in terms of operator protection and potentially reducing the risk of microbial contamination of prepared doses.

There are several designs of CSRD are available and risk assessment before use of these products should include an assessment of available validation data for both microbial and operator protection together with an assessment of suitability for the specific mAb product to be handled. This assessment should draw on suitably trained and experienced pharmacy staff and

should also consider the ease of use of the device and any potential risks of in use errors that may be introduced.

CSRDs can add significant unit cost to products and it must be remembered that even with the use of such devices, all vials in clinical areas should strictly be regarded as single use only.

Preparation Areas

Where preparation is to take place in a clinical area, there must be a clearly defined dedicated, well ventilated preparation area available of a suitable size to accommodate the expected workload and type of activity. This should have adequate bench space to allow segregation of activities where more than one person may be working at any given time. The area should not be a thoroughfare. A Standard Operating Procedure (SOP) should be in place to describe the cleaning down the area before and after each use using appropriate agents. Bench construction materials should be easy to clean and resistant to any cleaning agents used. Preparation areas should also be fully cleared after each product is prepared and labels should be added to the finished product on completion to allow each prepared dose to be identified in cases where the drug is not prepared as a single item and administered immediately to the patient. Procedures should be in place for dealing with spillages and suitable materials and equipment available to clear up after any spillage of mAB.

Procedures and Training

Appropriate SOPs should be in place describing the preparation of each product following aseptic non touch technique (ANTT). All staff preparing mAb products should be specifically trained in each of these SOPs and this training recorded.

Pharmacy departments that have aseptic preparation units will be in a position to provide specific expert training in good aseptic preparation technique to minimise the risk of contamination and errors and should be used as a resource for providing this training to nursing staff preparing mAb products in clinical areas.

Trust Policy on handling of mAbs.

It is recommended that all Trusts have in place a policy for the handling of mAbs. This should describe the responsibility of the Chief Pharmacist in defining the requirements needed for mAbs prepared outside the pharmacy, the resources available for handling of mAbs within the organisation, the mechanisms in place for the risk assessment of MAB handling and the clinical areas where mAbs may be used.

This should be endorsed at Board level within the Trust and include a commitment to provide the resources necessary to allow the safe preparation of mAbs within the Trust in line with the guidance included within this document. It should also address the subject of the cost of provision of the resources required and how these are linked to the costs passed on to commissioners.

References

1. Control of Substances Hazardous to Health Regulations 2002.
2. National Patient Safety Agency Alert 20, March 2007
3. European Standard EN 149:2001 Filtering Half masks to protect against particles

Document History	Issue date and reason for change
Version 1	Issued – NHSPQAC response to handling queries
Version 2	July 2003 – updated and issued as NHSPQAC yellow cover document
Version 3	June 2004 – updated and issued as joint NHSPQAC / PASG / BOPA document
Version 4	January 2008 – updated to reflect ongoing experience and NPSA Alert 20
Version 5	November 2015 – updated to reflect queries raised about preparation in clinical areas and wider product range
Version 6	