Position Statement:
2022 update to the safe handling of monoclonal antibodies in healthcare settings

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ABSTRACT

Aim

The aims were to (a) review the scientific literature on occupational risk, including exposure mechanisms and risk assessment, with regards to handling monoclonal antibodies (mABs) in healthcare settings; and (b) update the recommendations in the Clinical Oncology Society of Australia (COSA) safe handling of monoclonal antibodies in healthcare settings position statement, published in 2013.

Methods

A literature search was conducted between April 24, 2022, and July 3, 2022, to identify evidence relating to occupational exposure and handling of mABs in healthcare settings. Evidence in the literature was compared to the Position Statement published in 2013, and any potential additions, deletions, or revisions were discussed by the authors, and then agreed changes were made.

Results

Thirty-nine references were included in this update, comprising of the 2013 Position Statement itself and 10 of its references, as well as 28 new references. The risks to healthcare workers in the preparation and administration of mABs arise from four distinct exposure mechanisms: dermal, mucosal, inhalation, and oral. Updates included recommendations on using protective eyewear during the preparation and administration of mABs, developing a local institutional risk assessment tool and handling recommendations, considerations for using closed system transfer devices, and to have awareness of the nomenclature change from 2021 for new mABs.

Conclusion

Practitioners should follow the 14 recommendations to lower occupational risk when handling mABs. Another Position Statement update should occur in 5–10 years to ensure the currency of recommendations.

1. Introduction

The first Clinical Oncology Society of Australia (COSA) Safe Handling of Monoclonal Antibodies in Healthcare Settings Position Statement was published in 2013.[1] Since then, many new monoclonal antibodies (mABs) have been registered for use. mABs have unique characteristics in terms of chemistry, pharmacology, biological activity, toxicity, and formulation[2, 3] and may pose an occupational exposure risk to healthcare workers who prepare or administer them or who work in areas where they are administered.[1-16]

Compared to the plethora of guidelines for the safe handling of cytotoxic medication, up-to-date guidelines for the safe handling of mABs are lacking. Without an understanding of risks, healthcare workers may have concerns regarding the safe handling of mABs, such as whether they should be prepared under controlled conditions (i.e., from a centralized service such as a pharmacy cleanroom) or can be prepared on the ward.[10] These concerns are extrapolated from published studies with cytotoxic medicines which have shown that workplace exposures to hazardous drugs can cause both acute and chronic health effects.

In response to these concerns, consensus guidelines on occupational risk with handling mABs in healthcare settings have been published in the past several years. These publications reflect the enthusiasm of organizations in committing their own resources to define occupational risk and mitigation, where scientific and regulatory guidance is lacking. In addition, a 2016 survey of healthcare workers in Australia revealed the importance of independently produced guidelines (external regulatory or professional body guidelines) for the handling of mABs.[4] With this support for organization-led guidance it was timely the COSA Position Statement was reviewed to ensure currency of information and recommendations. This updated Position Statement can be used by healthcare institutions to review occupational risk and define mitigation strategies in handling mABs.

2. Method

A literature search was conducted between 24th April 2022 and 3rd July 2022 to identify published evidence relating to occupational exposure and handling of mABs in healthcare settings. The medical databases used were MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PubMed. The subject terms searched in MEDLINE and CINAHL, were “Monoclonal antibodies” and “Occupational Exposure”, as well as “Monoclonal antibodies” and “Handling”. In PubMed, a literature search was conducted using Medical Subject Heading (MeSH) terms “Monoclonal antibodies” and “Occupational Exposure”, MeSH terms “Monoclonal antibodies” and Text Word term “Handling”. The reference lists in the identified literature from the search methodology were also reviewed, as was the reference list from the 2013 Position Statement, to confirm literature currency and relevancy. In addition, any other relevant publications known to the authors but not identified from the above means were also considered for inclusion. The literature was reviewed by a minimum of two authors. Evidence in the literature was compared to the Position Statement published in 2013, and any potential additions, deletions, or revisions were discussed by the authors, and then agreed changes were made. This Position Statement was endorsed by the COSA Cancer Pharmacists Group on 27 September 2022 and subsequently, by the COSA Council on 1 November 2022.

3. Results

From the literature search, 39 references were included in this update, comprising the 2013 Position Statement itself and 10 of its references, as well as 28 new references. The literature identified outside of the database search included the New Zealand Nurses Organisation (NZNO) Position Statement[6], the eviQ Safe Handling and Waste Management of Hazardous Drugs clinical resource[8], and the updated COSA Guidelines for the Safe Prescribing, Dispensing and Administration of systemic cancer therapy were retrieved from the individual organization's website.[15] In addition, the current National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic Drugs and Other Hazardous Drugs in Healthcare Settings[13] (2016) and the proposed 2020 draft NIOSH List of Hazardous Drugs in Healthcare Settings[14] were retrieved from the US Centres for Disease Control and Prevention website and were also included. Furthermore, two further references familiar to the authors were also included − the Victorian Therapeutic Advisory Group (VicTAG) Victorian Framework Handling of Hazardous Medicines 2021[16] and a publication on the new nomenclature for mABs.[17] Six references from the 2013 Position Statement were removed as they were deemed to be no longer required or they were superseded by an updated version.

A review of the literature revealed limited evidence of occupational exposure risk associated mABs. However, since the first COSA Position Statement, several consensus guidelines and position statements for the safe handling of mABs have been published,[3, 6-8] as well as review papers[9, 10, 12] and commentary[11] on the occupational exposure risks. Among the relevant literature published since the 2013 Position Statement, literature relating specifically to pertuzumab,[13, 14] closed system transfers devices (CSTDs) used with mABs,[3, 18-22] a case report relating to staff sensitization to a mAB[5], and the nomenclature change to mABs,[17] was identified.

Pertuzumab is included in the current (2016) NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings as a hazardous drug based on reproductive and developmental toxicity.[13] However, it has been proposed to remove pertuzumab from the draft 2020 update, as NIOSH has determined it is unlikely for pertuzumab to pose a reproductive threat to workers in healthcare settings.[14] Another proposed change to the NIOSH 2020 List of Hazardous Drugs in Healthcare Settings is the addition of blinatumomab based on the observed neurotoxicity at low doses in patients in clinical studies.

In the last few years, there have been several papers published relating to the use of CSTDs in the preparation and administration of mABs.[18-22] While CSTDs provide enhanced protection against potentially hazardous exposures to healthcare workers,[3, 13] performance standards for evaluation of CSTD containment are not yet available.[23] Several publications on device performance have been published, with issues identified including vapor containment[19] and unintended volume loss associated with small-volume products.[18, 21, 22]

Insoluble fine particles in the final product were detected when CSTDs were used in the preparation of mABs, but the clinical significance of this finding is uncertain.[20, 21] Institutions should consider these potential issues when selecting CSTDs.

Recently, the World Health Organization (WHO) international non-proprietary names (INN) expert group revised the nomenclature of mABs.[17] The revised system was adopted in 2021, with the main provocative change to discontinue the use of the well-established suffix –mab. This will now be replaced by four new suffixes. The new suffixes include -tug, -bart, -mig, and -ment. The application of these suffixes with the different types of mABs is described below:

1. tug is used for full-length, monospecific, and Fc unmodified immunoglobulins.
2. bart is used for full-length, monospecific, immunoglobulins with engineered constant domains.
3. mig is used for bispecific or multi-specific immunoglobulins, regardless of their format, type, or shape.
4. ment is used for monospecific fragments of any kind that are derived from an immunoglobulin variable domain.

3.1. Risk exposure mechanisms

The risks to healthcare workers in the preparation and administration of mABs arise from four distinct mechanisms: dermal exposure, mucosal exposure, inhalation exposure, and oral (intake) exposure.[1, 9] The exposure mechanisms described below assume that the preparation technique has occurred in line with the Product Information (PI) recommendations and Good Manufacturing Practice, and hence the integrity of the mAB is not compromised.

3.2. Dermal exposure

The skin is an effective barrier to the absorption of high molecular weight proteins. The upper limit for dermal absorption of compounds is around 500 Da to allow penetration of the stratum corneum.[24] Given that mABs have a much higher molecular weight (usually greater than 140 kDa) the potential for dermal uptake of intact skin of unconjugated mABs or intact conjugates in the occupational setting is unlikely.[25] As mABs are immunoglobulin based they would also have restricted access across diffusional barriers unless transport is facilitated by specific mechanisms.[26] However, skin conditions such as dermatitis and other damage to the skin may facilitate the dermal uptake of mABs.[25]

3.3. Ocular exposure

A type of mucosal exposure is ocular exposure. In an animal study, anti-CD4 mAB in a liposomal formulation applied topically has been shown to prolong graft survival in orthotopic corneal allografts.[27] The amount of exposure is 45mcg/day for 10 days which may present low-dose occupational exposure. Another study has shown that topically applied mAB can accumulate in the retina and exert pharmacological effects.[28] The use of protective eyewear by healthcare personnel when handling mABs can minimize ocular exposure, and while not proven, may in turn minimize the potential for health hazards.[3]

3.4. Inhalation exposure

The greatest risk of exposure during the preparation of mABs is through inhalation of aerosols. However, even this risk is low. Aerosolized cetuximab in a mouse model has shown that the airway barriers are permeable to mABs, but their passage into the bloodstream is limited.[29] Estimates on the bioavailability of high molecular weight substances (>40 kDa) have been at 5% by inhalation.[30] However, given the high molecular weights of mABs, the absorption rates could be considered lower. In areas where mABs may be administered to patients via inhalation, the potential for exposure to the worker may be increased.[31] Currently, there are no mABs registered for use via the inhalation route in Australia.

When considering the risk of inhalation exposure, it is important to consider the potential for the drug to cause direct effects on the lung. Examples of mechanisms of direct effects are via the target receptor present in the lung, or by pulmonary vasodilator effects. In this instance, the pharmacologic effects would not be dependent on systemic bioavailability.[12]

Furthermore, as mABs are proteinaceous products, it is possible for healthcare staff to experience sensitization and an allergic reaction to these medicines. An example published in a case report described how a nurse became sensitized to bevacizumab as a result of preparing and administering mABs in a clinical area.[5] Despite the hospital policy to wear a mask among other personal protective equipment (PPE), the nurse was not wearing a mask at the time of her reaction which included a sudden onset headache and feeling faint and shaky. The allergist concluded the symptoms could have been potentially due to aerosolized exposure to bevacizumab.

3.5. Oral exposure

Oral exposure of mABs through hand-to-mouth transmission may occur. mABs are intricately folded proteins that are easily susceptible to denaturation from environmental conditions.[32] If ingested, mABs are rapidly broken down by gut enzymes and acids resulting in denaturing of the protein and loss of biological activity. Exposure via this route would be minimal.[25] However, there may be a theoretical risk from resultant lower molecular weight mABs from conjugates which may be absorbed systemically.

3.6. Risk assessment

In the absence of occupational health studies, occupational risks from mABs have been extrapolated from the side effects of therapeutic doses, and risk assessment models and flowcharts have been developed.[2, 3, 10, 25] One publication prepared a risk assessment tool based on the antigenic properties and the toxic potential of mABs.[2] Another evaluated the reproductive and developmental toxicity and effects on fertility of several mABs.[25] While the evidence was lacking, the authors concluded that all mABs evaluated had the potential for some level of reproductive toxicity.

The Australian consensus guidelines for the safe handling of mABs published a risk assessment model and flowchart for institutions to consider and evaluate clinical and operational factors unique to their individual healthcare settings[3]. In 2019, a flowchart for risk assessment and allocation of preparation of mABs was published by Bauters et al.[10] This flowchart was developed based on toxicity profile (cytotoxicity and developmental/mutagenic/fertility toxicity) as well as practical and financial considerations such as vial sharing, formulation factor, and staff experience.

Moreover, there is no evidence that mABs cannot achieve a detectable level in humans following repeated occupational exposure.[11] This suggests repeated long-term occupational exposures of therapeutic mABs to healthcare workers should be kept to a minimum,[11, 12] however, the definition of 'repeated long term' is unclear. Appropriate use of PPE must be used to protect healthcare workers handling mABs in healthcare settings. The recommendations are underpinned by the assumption that PPE is being correctly worn, and that repeated accidental exposure does not occur due to rigorous training around the safe handling of mABs.[7] Finally, an analytical method to detect airborne antibodies has been described in the literature; however, its application in practice is unclear as there is no defined occupational exposure limit for each mAB.[33]

Based on the risk exposure routes and risk assessment information above, recommendations for the safe handling of mABs are described below.

3.7. Position Statement Recommendations

1. These recommendations do not replace clinical guidelines for the safe prescribing, dispensing, and administration of cancer chemotherapy.[15]
2. The information available on the occupational toxicity of mABs is limited.[7, 25] Each institution should be guided by professional bodies as new information becomes available. This is especially important when handling newer mABs or mABs used in the clinical trial setting.
3. Staff preparing and administering mABs should be competent in aseptic transfer techniques. Some mABs require complex dosing calculations or complex reconstitution techniques.[4, 7] Proteins are easily broken down with excessive shaking[4] and may froth when reconstituted. Staff must be offered training (and ideally undertake competency assessment) in the preparation of these medicines.[1]
4. It is preferable that the task of preparation be performed by a centralized service. Where mABs are prepared by a centralized service, they should be prepared according to accepted standards.[7, 34, 35]
5. Where mABs are prepared by a centralized service in the same safety cabinets as cytotoxic agents, appropriate cleaning and decontamination should occur between preparations of cytotoxic agents and mABs. If this is not possible, a CSTD should be used for the preparation of all cytotoxic medicines to minimize surface contamination of the end product.[36] In all other situations, the use of such devices should not be considered mandatory.[3]
6. Institutions utilizing a CSTD should consider user experience and technique. They must also evaluate the device(s) to ensure that when correctly used, protein aggregation does not occur, the medication is compatible with the components of the CSTD [19, 20, 22], and there are no significant small volume losses during the reconstitution process or administration.[18, 21]
7. When preparations of mABs occur outside a centralized service as determined by institutional risk assessment, it should occur in a dedicated area away from patients and carers to minimize unnecessary exposure.[1]
8. It is expected that many more mABs will be approved for use in the future. Each institution should develop its own risk assessment tool and handle recommendations based on current scientific literature (including production information, the product safety data sheet, and investigator information for clinical trial mABs) and operational factors.
9. Precautions taken during the preparation and administration of mABs, such as protective eyewear (except, for preparation, if eye protection is already afforded by way of the cleanroom facilities e.g., isolator), handwashing, wearing gloves, face masks, backed up with robust surface cleaning of handling areas, are likely to reduce potential risks further.[8, 37] In the event of needle stick injury or a spill, institutional guidelines should be followed.

10. Disposal of waste products associated with mABs should be in accordance with the disposal of clinical waste. This applies to waste production during preparation and administration, as well as patient waste.[3]
11. Any mABs conjugated to a cytotoxic agent must be considered hazardous. Preparation and administration of these medicines must follow accepted cytotoxic safe handling precautions.[7, 8]
12. Any mABs conjugated to a radioisotope must be considered hazardous. Preparation and administration must be in accordance with regulations regarding the handling of radiopharmaceuticals.[7, 8]
13. These recommendations should be applied to other complex proteins, such as fusion proteins.[1]
14. Practitioners should be aware of the suffixes -tug; -bart; -mig; and -ment adopted for new mABs from 2021 when reviewing the safe handling of these medicines to understand they are mABs.[17]

4. Discussion

A review of the literature revealed some changes required to the Position Statement (see Table 1). The 2013 version contained 10 recommendations, while the updated Position Statement contains 14. As expected, there was limited literature on occupational exposure risk associated mABs identified, as the design of experiments on humans would be unethical. The occupational risk reviews published were based on the extrapolation of occupational-related toxicity from data obtained in therapeutic situations.[2, 10, 25] This information alone may be misleading. Potential exposure pathways as discussed above were either not considered or the authors concluded that exposure via these pathways would be very minimal. Any data extrapolated in this setting should be critically analyzed factoring in aspects of routes of potential exposure.

TABLE 1. Outline of changes to content from the 2013 Position Statement compared to the 2022 Position Statement

2013 Position Statement recommendations including recommendation number	**Outline of any update in the 2022 Position Statement recommendations and corresponding recommendation number**
1. These recommendations do not replace clinical guidelines for the safe prescribing, dispensing, and administration of cancer chemotherapy.	1. No update
2. The information available on the occupational toxicity of mABs is limited. Each institution should review its handling procedures and be guided by professional bodies as new information becomes available. This is especially important when handling newer mABs or mABs used in the clinical trial.	2. Very minor update to the final sentence. The word setting was added following the words “clinical trial” so that it now reads “clinical trial setting.”

3. Staff preparing and administering mABs should be competent in aseptic transfer techniques. Some mABs require complex dosing calculations or complex reconstitution techniques. Proteins are easily broken down with excessive shaking and may froth when reconstituted. Staff must be offered extra training in the preparation of these agents.	3. Minor change to the last sentence. It now reads: Staff must be offered training (and ideally undertake competency assessment) in the preparation of these medicines.
4. It is preferable that the task of preparation be performed by a centralized service. Centralizing preparation may also minimize expenditure. Where mABs are prepared by a centralized service, they should be prepared according to accepted standards	4. Minor change. The sentence "Centralising preparation may also minimize expenditure" has been removed due to cost not being a focus of the Position Statement. It now reads: It is preferable that the task of preparation be performed by a centralized service. Where mABs are prepared by a centralized service, they should be prepared according to accepted standards.
5. Simple precautions taken during the preparation and administration of mABs, such as hand washing, wearing gloves and face masks, backed up with robust surface cleaning of handling areas are likely to reduce potential risks further. Preparation should occur in a dedicated area away from patients and carers.	9. Significant change to reflect the inclusion of protective eyewear (this is in line with our current understanding and evidence regarding the occupational risk arising via ocular exposure and is consistent with the Australian Consensus Guidelines) and reference to needle stick injury and spill. The recommendation now reads: Precautions taken during the preparation and administration of mABs, such as protective eyewear (except, for preparation, if eye protection is already afforded by way of the cleanroom facilities e.g., isolator), handwashing, wearing gloves, face masks, backed up with robust surface cleaning of handling areas, are likely to reduce potential risks further. In the event of a needle stick injury or a spill, institutional guidelines should be followed. The sentence regarding preparation in a dedicated area has been omitted and included as a separate recommendation (recommendation 7), due to it being a separate topic.
6. Where MABs are prepared by a centralized service in the same safety cabinets as cytotoxic agents, appropriate cleaning and decontamination should occur between preparations of cytotoxic agents and MABs. If this is not possible, a closed-system drug transfer device should be used for the preparation of all cytotoxic items to minimize surface contamination of the end product. In all other situations, the use of such devices should not be considered mandatory.	5. No update.
7. Disposal of waste products associated with MABs should be in accordance with the disposal of clinical waste. This applies to waste production during preparation and administration, as well as patient waste.	10. No update.
8. Any MABs conjugated to a cytotoxic agent must be considered hazardous. Preparation and administration of these	11. Very minor update, change of word "agents" to "medicines" in the second sentence. The recommendation now reads: Any mABs conjugated to a cytotoxic agent must be considered hazardous. Preparation and administration of these

agents should follow accepted cytotoxic safe handling precautions.	medicines must follow accepted cytotoxic safe handling precautions.
9. Any mABs conjugated to a radioisotope must be considered hazardous. Preparation and administration must be in accordance with regulations in regard to handling radiopharmaceuticals	12. No update.
10. Similar consideration should be given to other complex proteins, such as fusion proteins.	13. Very minor update to the sentence to omit the words "similar considerations" and reflect stronger language. The sentence now reads: These recommendations should be applied to other complex proteins, such as fusion proteins. 6. New recommendation. Institutions utilizing a CSTD should consider user experience and technique. They must also evaluate the device(s) to ensure that when correctly used, protein aggregation does not occur, the medication is compatible with the components of the CSTD, and there are no significant small volume losses during the reconstitution process or administration. 7. When preparations of mABs occur outside a centralized service as determined by institutional risk assessment, they should occur in a dedicated area away from patients and carers to minimize unnecessary exposure. 8. New recommendation. It is expected that many more mABs will be approved for use in the future. Each institution should develop its own risk assessment tool and handle recommendations based on current scientific literature (including production information, the product safety data sheet, and investigator information for clinical trial mABs) and operational factors. 14. New recommendation. Practitioners should be aware of the suffixes -tug; -bart; -mig; and -ment adopted for new mABs from 2021 when reviewing the safe handling of these medicines to understand they are mABs.

Regarding risk assessment, the flowchart published by Bauters et al.[10] to determine the site for mAB product preparation (pharmacy cleanroom or on the ward), has its limitations. These limitations included no consideration of the requirements for clinical trial medicines (e.g., the trial may stipulate a minimum standard for preparation) and patient-specific medication access program medicines (e.g., loss of dose if a vial is accidentally broken; a medication error may occur during preparation due to the increased risk of interruption/distraction from preparation on the ward). In addition, it may be preferred to prepare expensive mABs in the pharmacy to manage the financial risks of accidental loss of vial(s) or preparation error.

In terms of the proposed addition of blinatumomab to the NIOSH 2020 list of hazardous drugs based on the observed neurotoxicity at low doses in patients in clinical studies, this could be extrapolated as an occupational risk due to these low-dose effects.[14] While blinatumomab does have a low molecular weight (54 kDa) compared to other mABs, it is unlikely the occupational risk would arise from the dermal route with intact skin.

A limitation of this current review is that the individual PI and Safety Data Sheet (SDS) for each mAB registered in Australia has not been reviewed. The rationale is that both PIs and SDSs are continually being updated, therefore, it is recommended healthcare workers review individual PIs and SDSs as necessary. Another limitation is the scarcity of published scientific literature on potential health hazards associated with repeated occupational exposure to mABs. Only one published case report on staff sensitization to therapeutic mABs resulting from workplace exposure was identified.[5] It is unclear whether this reflects the minimal risk of health hazards associated with the preparation and administration of mABs by healthcare workers based on current handling practice, or the latency of mAB toxicity associated with long-term repeated occupational exposure.

This literature review has clearly demonstrated the lack of post-marketing surveillance for mABs including occupational exposure and toxicity quantification information. If a healthcare worker has an adverse reaction to an mAB from occupational exposure, it is required to be reported to the relevant governing body, in the case of Australia, the Therapeutic Goods Administration.[38] The adverse reaction should also be reported to the medicine sponsor.[39] In turn, the medicine sponsor is required to report all serious adverse reactions as part of pharmacovigilance responsibilities. Serious adverse reactions include reactions that are deemed a "medically important event or reaction". As post-marketing surveillance is lacking with occupational exposure, it seems prudent that this statement would include all occupational exposure adverse reactions.

5. Conclusion

Since the first Position Statement was published in 2013, clinical practice has evolved alongside the increased use of mABs. This almost extra decades' worth of experience with mABs has contributed to informing important changes to the Position Statement. Namely, with regards to the recommended use of protective eyewear during the preparation and administration of mABs, the development of a local institutional risk assessment tool and handling recommendations, considerations for using CSTDs, and the mAB nomenclature change. With increased interest in the safe handling of mABs, it is anticipated that new scientific findings on the occupational risks associated with their preparation and administration will emerge. We encourage healthcare workers to report post-marketing surveillance information of registered mABs including occupational exposure and toxicity quantification as discussed above. Such information will provide insight into the occupational risk and assessment of handling mABs in healthcare settings in the future. Another Position Statement update should occur in five to ten years to ensure currency of recommendations or sooner depending on scientific and other literature that may emerge.

About COSA and the CPG

The **Clinical Oncology Society of Australia** (COSA) is Australia's peak multidisciplinary society for health professionals working in cancer research, treatment, rehabilitation and palliative care with over 1000 members. COSA is an advocacy organisation whose views are valued in all aspects of cancer care. COSA provides high-level clinical advice to Cancer Council Australia.

The **Cancer Pharmacists Group** (CPG) is a group of COSA comprised of pharmacists practising in a variety of settings including medical oncology, haematology, palliative care and cytotoxic preparation services. The CPG provides the only national multidisciplinary forum for pharmacists working in cancer services.

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