Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel

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Authorship

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Foreword

This work was completed as part of a Western and Central Melbourne Integrated Cancer Service (WCMICS) funded project.

The current guidelines provide recommendations relating to the safe handling (preparation, administration and waste disposal) of monoclonal antibodies. Definitive recommendations are given for the minimum safe handling requirements to protect healthcare personnel. A risk assessment model is provided for institutions to consider and evaluate clinical and operational site-specific factors. In formulating these guidelines, best available evidence relating to occupational health and safety risk as well as clinical risk and other operational factors were considered. These guidelines specifically evaluate monoclonal antibodies used in the Australian cancer clinical practice setting however principles may be applicable to monoclonal antibodies used in non-cancer settings. The guidelines are only applicable to parenterally administered agents.

Conflicts of Interest

These guidelines were produced independently by members of the project writing group. The following members are consultants or advisory committee members or receive honoraria, fees for service, or travel assistance (independent of research-related meetings) from; or have research or other associations with the organizations listed: Ashish Bajel – MerckSharpDohme, Novartis, Sanofi-Aventis; Peter Fox – Roche; Michael Green – Roche, Sandoz; Sue Kirsa – Roche, Sandoz, Amgen, Orion, Perigo, Novartis; Senthil Lingaratnam – Roche, Sanofi-Aventis; Julie Wilkes – Chemo@home, SHPA, Leukaemia Foundation, Roche, Amgen, Bristol Myers Squibb, Jannsen

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Executive Summary

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). MABs either do not fulfil hazardous drugs criteria or lack sufficient agent-specific information to assign an appropriate hazard classification. Industry standards for correct handling and exposure risk associated with MABs are conflicting or out-dated. Operational and clinical issues (e.g. vial-sharing, preparation complexity and medication error risk) also influence how MABs are handled. This often results in 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 the Australian healthcare context. This guideline does not provide prescriptive recommendations for the preparation and handling of MABs due to the many influencing clinical and operational factors unique to healthcare centres. Rather, the guideline provides a mechanism for individual institutions to assess these factors. The guideline does however provide clear recommendations of agreed minimum safe handling requirements to protect healthcare personnel. Recommendations are based largely on an absence of data supporting a practice in the face of potential harm to healthcare personnel.

Section 1 of this document provides an introduction to the background and development to these *Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel.*

Section 2 offers recommendations for the appropriate handling of MABs by healthcare personnel in the cancer services setting. Recommendations are summarised on pages 6 and 7 of this document (table 1), with supporting evidence for each recommendation presented in the body of section 2. Occupational health, operational and clinical factors have been considered in formulating each of the recommendations.

Sections 3 to 5 provide guidance on how to use these guidelines when considering biosimilar products (section 3), MABs for non-malignant diseases (section 4), and MABs conjugated to another hazardous substance (section 5).

Section 6 provides practical examples on how the guideline recommendations can be applied in the clinical practice setting.

To develop th*ese Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel*, a multidisciplinary steering committee (SC) was formed with representatives from Peter MacCallum Cancer Centre, Royal Melbourne Hospital, St Vincent's Hospital, Western Health, Western and Central Melbourne Integrated Cancer Service (WCMICS), and relevant experts. The role of the SC was to provide oversight of project activities. Two project officers were appointed to undertake the project work. A multidisciplinary writing group (WG) was formed and endorsed by the SC to develop and write the guidelines. The WG reviewed existing MAB handling guidelines to determine research questions, develop the structure of this guideline and also to direct the literature searches undertaken for each recommendation.

The guidelines were developed in accordance with the principles outlined by the National Health and

Medical Research Council (NHMRC) guide to the development, evaluation and implementation of clinical practice guidelines.[1] The recommendations made in this guideline document are strengthened by a rigorous methodology, informed through critical appraisal of the available literature. For many recommendations, there was a paucity of high quality supportive evidence with a predominance of pre-clinical evaluations, animal studies and expert opinion.

In formulating the recommendations for this guideline, the committee recognised and took into account a number of factors and limitations pertaining to the available evidence base. Despite numerous studies looking at the various toxicities associated with MABs, the results related most frequently to animals not humans. Where human studies were considered, there was concern within the WG about how findings relating to therapeutic doses may be extrapolated to low level, long term occupational exposure given the lack of evidence in this area. Studies investigating the stratification of exposure risk and safety interventions typically considered traditional cytotoxic chemotherapy agents, again raising questions about how to translate these findings into the MABs handling setting.

Each of the seven recommendations in this document were assigned a grade and level according to defined NHMRC criteria.[2] Where clinical evidence was lacking but consensus existed among WG members, consensus-based recommendations were given. Such recommendations have been categorised as Good Practice Points (GPPs). The recommendations were formulated using a considered judgement process, taking into account the amount and quality of available evidence, as well as its generalisability and applicability in the Australian setting.

In framing the guideline recommendations, the WG has carefully considered the need to balance occupational health with clinical and operational factors associated with the preparation of MABs. The results of an Australian national survey of clinicians recognised that both occupational health and non-occupational health issues were important factors to consider when determining how and where a MAB should be prepared.[3]

Summary of Recommendations

Table 1 - Summary of Recommendations

	Recommendation	Level-Grade*	Section
I.	That the occupational health and safety risk to healthcare personnel handling MABs is dependent on the following risk factors:		**2.1**
	i. Internal Exposure Risk		
	via dermal absorption	GPP	2.1.1
	via inhalation absorption	GPP	2.1.2
	via mucosal absorption	GPP	2.1.3
	via oral absorption	IV-D	2.1.4
	ii. Toxicity		
	cytotoxicity	GPP	2.1.5
	carcinogenicity	II-C	2.1.6
	genotoxicity or mutagenicity	GPP	2.1.7
	teratogenicity or other developmental toxicity	IV-D	2.1.8
	organ toxicity at low doses	GPP	2.1.9
	immunogenicity	III-D	2.1.10
II.	From an occupational health and safety perspective, it would be prudent for MABs to require greater handling precautions than other non-hazardous injectable medications however they do not warrant full cytotoxic precautions, with exceptions only where sufficient evidence exists of safety concerns for a specific MAB.	GPP	**2.2**
III.	Safe handling procedures should be stratified according to:		**2.3**
	i. Healthcare staff role (preparation, administration, transportation/disposal)	III-D	2.3.1
	ii. Health considerations (e.g. pregnancy)	GPP	2.3.2
IV.	Procedures for the handling of waste generated during the preparation or clinical use of MABs are as follows:		**2.4**
	i. Waste products generated during the preparation of MABs should be disposed as per standard operating procedures for parenterally administered agents, i.e. not classified as cytotoxic waste	GPP	2.4.1
	ii. Waste products and/or bodily fluids of patients who have been administered MABs should be disposed as per standard operating procedures for parenterally administered agents, i.e. not classified as cytotoxic waste	GPP	2.4.2
V.	The range of available interventions / safeguards to minimise occupational exposure are:		**2.5**
	i. Personal Protective Equipment (PPE)		2.5.1

*Level and Grades of evidence assigned according to NHMRC levels and grades of evidence.[2] Refer to table 2 for further explanation.

1. Introduction

1.1. Background

Monoclonal antibodies (MABs) play an important role in the treatment of both malignant and non-malignant diseases with more than 100 new MABs currently in development or undergoing regulatory review.[4] Whilst patients are benefiting from the rapid production and clinical utilisation of these agents, there is little information regarding the risks of occupational exposure for hospital personnel.

MABs are immunoglobulins (usually of the immunoglobulin G (IgG) class) comprised of two distinct fragments. The antigen-binding fragment (Fab) engages the tumour cell antigen whilst the crystalline fragment (Fc) binds to a receptor on an effector.[5] MABs are generated using biotechnologies including recombinant DNA (rDNA) or hybridoma technology, B lymphocyte immortalisation or other technologies (e.g. display technology, genetically engineered animals).

Unlike traditional anticancer agents, which fulfil criteria for classification as cytotoxic or hazardous substances, many new drug treatments either do not fulfil the same criteria[6,7] or there is insufficient agent-specific information as yet to assign an appropriate classification. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines (adopted by the Australian Therapeutic Goods Administration (TGA), American Food and Drug Administration (FDA) and the European Medicines Agency (EMA); MABs are not required to be evaluated for carcinogenicity or genotoxicity.[8]

Consequently, there is uncertainty about correct handling and exposure precautions of these agents. An Australian-wide clinical practices survey demonstrated that MABs were being handled according to cytotoxic standards (i.e. preparation within pharmacy clean room) in some institutions whereas other institutions applied limited safety precautions (i.e. preparation at the bedside).[3]

1.2. Clinical Need for Current Guidelines

Previously, there has been no standard for safe handling of MABs. Consequently cytotoxic standards have typically been applied when these molecules were used as part of cancer therapy. The health outcomes from occupational exposure of these molecules in pharmacy, nursing and medical staff are largely unknown. Given there is a paucity of published evidence that these molecules have any short or long term toxic effects following occupational exposure, application of cytotoxic standards to the handling of these molecules may have undue impact on reducing efficiency and increasing costs and time allocation in relation to resources required for preparation (pharmacy personnel time, consumables required, use of cytotoxic drug safety cabinets) and administration (appropriately trained nursing staff, treatment restricted to hospital only). Considerations around the need for aseptic preparation of doses, the complexity of dosing regimens and cost of vials have been absent in other guidelines. This has an impact beyond the cancer services setting affecting cardiology, rheumatology, neurology, immunology, gastroenterology, nephrology and non- malignant haematology where such molecules are also utilised. Current industry standards

either fail to address these issues for MABs or are conflicting. There is no consensus on the hazard categorisation of MABs. For example, (a) Worksafe Victoria 'Handling Cytotoxics in the Workplace' - January 2003 make no mention of MABs,[9] the National Institute for Occupational Safety and Health (NIOSH) guidelines 2012 do not list major anticancer MABs as meeting hazardous drug criteria,[7] (c) the International Society of Oncology Pharmacy Practitioners (ISOPP) standards of practice reference the NIOSH criteria for classification of hazardous drugs,[10] and (d) the Material Safety Data Sheets (MSDS) provided by pharmaceutical companies are conflicting and the information within a current MSDS may be out-dated. The Clinical Oncology Society of Australia (COSA) was the first national organisation to commence developing recommendations for the handling of MABs. The position statement '*safe handling of monoclonal antibodies in healthcare settings'* was produced by the Cancer Pharmacists Group (CPG), representing pharmacists from a variety of practice settings including medical oncology, haematology, palliative care and cytotoxic preparation services.[11]

Safe-handling to minimise or eliminate staff exposure is only one reason why these molecules may be prepared in hospital pharmacy clean-rooms. Considerations regarding aseptic technique to prevent accidental microbial contamination, complexity of dosing, maintenance of molecule integrity and financial expense (in order to reduce wastage) are also taken into account with decisions regarding bedside versus pharmacy preparation of these drugs.

1.3. Intended Users

These guidelines are intended to be used by healthcare personnel (medical, pharmacy and nursing) who are involved in the handling of MABs in cancer treatment. By providing a framework of recommendations, health care facilities can develop multidisciplinary safe handling procedures of MABs, which lead to improved institutional efficiency while optimising patient and staff health outcomes.

1.4. Scope

Recommendations within this guideline were developed specifically for MABs used in the cancer services settings. MABs used in non-malignant diseases and those in early development clinical trials were not formally evaluated in the development of these guidelines. Recommendations exclude MABs conjugated to cytotoxic, radioactive or other hazardous compounds, which should be handled according to relevant procedures for the conjugated agent. Principles from which recommendations were made are deemed to be relevant to the non-cancer setting, however further evaluation and risk assessment in these settings may be required. Recommendations are applicable to biosimilar products.

1.5. Methods of Guideline Development

The process for guideline development was conducted in accordance with principles outlined by National Health and Medical Research Council (NHMRC) and Turner.[1,12]

1.5.1. Funding

The guideline development project was funded by Western and Central Melbourne Integrated Cancer Service (WCMICS).

1.5.2. Governance

A multidisciplinary SC was formed with representatives from Peter MacCallum Cancer Centre, Royal Melbourne Hospital, St Vincent's Hospital, Western Health, Western and Central Melbourne Integrated Cancer Service (WCMICS) and relevant experts in the field of cancer medicine (Appendix 2). The role of the SC was to provide oversight of project activities. Two project officers (oncology pharmacists), were appointed to undertake the project work. A guideline WG comprising of three medical oncologists, a haematologist, two oncology nurses, four oncology pharmacists and a consumer representative, was formed and endorsed by the SC to develop and write the guidelines (Appendix 3).

1.5.3. Description of current practices

Oncology pharmacists, medical oncologists, haematologists and senior nursing staff who were members of peak body oncology pharmacy, medical and oncology nursing associations were invited to participate in an on-line Australia-wide survey. The survey was sent to the Cancer Nurses Society of Australia (CNSA), Clinical Oncological Society of Australia (COSA), Haematological Society of Australia and New Zealand (HSANZ), Medical Oncology Group of Australia (MOGA), and the Society of Hospital Pharmacists of Australia (SHPA). Survey respondents from across states and territories (n=222) represented their attitudes and institution practices regarding the preparation and administration of MABs, availability of institutional guidelines, and reasons/rationale (if known) for supporting such practices. The survey findings describe the range of current clinical practices, and aimed to identify particular trends across various sectors: public/private, regional/metropolitan, and size/type of the treatment facility. Survey findings provided context for the development of recommendations presented herein. Detailed methodology and results from the survey have be reported separately.[3]

1.5.4. Synthesis of evidence

Two project officers independently undertook a comprehensive search of the literature, assessed the eligibility of identified studies, critically appraised and summarised included studies. The literature search was undertaken between March and September 2013 using the following electronic databases: Medline (OVID), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Wiley Interscience, Embase, Pubmed, Cochrane Library and Google . Searches were conducted using both Medical Subject Heading (MeSH) terms and text words. The MeSH term monoclonal antibodies, was selected and initially exploded to include all subheadings. The search was then refined by combining the following text words: administration, exposure, guidelines, handling, metabolism, pharmacokinetics, pharmacology, physiology, poisoning, or safety. The reference lists of relevant papers were also searched. Pharmaceutical company information including product information (PI) sheets, material safety data sheets (MSDS) and unpublished data were searched for drug

specific information. Detailed methodology and results from the literature review have be reported separately.[13]

1.5.5. Levels and Grades of Evidence

The WG formulated seven major recommendations. Each recommendation was evaluated against NHMRC criteria (table 2) and where relevant assigned a grade and level.[2] The NHMRC criteria allowed the WG to differentiate between the strengths (grading) of their recommendations by taking into account the volume, consistency, clinical effect, generalisability and applicability of the supporting evidence. Where evidence was insufficient to meet even the lowest level of evidence (i.e. pre-clinical studies) or where no evidence was identified, consensus-based recommendations are given and annotated as Good Practice Points (GPP).

Table 2– Grades and levels of evidence (adapted from NHMRC)[2]

Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in application
D	Body of evidence is weak and recommendation must be applied with caution
GPP	Good Practice Point: recommendations where no gradable evidence was identified but wher committee members reached consensus
Level	**Description**
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls (non-randomised experimental trial, cohort st control study, interrupted time series with a control group)
III-3	A comparative study without concurrent controls (historical control study, two or more singl study, interrupted time series without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes

1.5.6. Process for reaching consensus

A summary of the findings of the survey along with the results from the literature search, were presented to the WG for formulation of draft recommendations, to the SC, and to attendees at subsequent consensus meetings. Two consensus meetings were held in Melbourne in August 2013. The meetings were attached to Australian conferences from the Medical Oncology Group of Australia (MOGA) and the International Society of Oncology Pharmacy Practitioners (ISOPP). Medical, pharmacy and nursing representatives were invited to attend the consensus meetings, with no requirement for conference registration or attendance. At each meeting consensus opinion was invited for all recommendations presented by the WG.

1.5.7. Consultation and endorsement

Draft recommendations developed at the consensus meetings were endorsed by the SC, and subsequently developed for publication. Clinical practice guidelines endorsed by professional body associations are more likely to be taken up by clinicians and healthcare services.[1] Accordingly, these guidelines were submitted to relevant professional body associations for final endorsement.

These *Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel* have been endorsed by the following listed associations: Association of Hospital Pharmacists (AHP), Cancer Nurses Society of Australia (CNSA), Clinical Oncology Society of Australia (COSA), COSA Cancer Pharmacists Group (CPG), Medical Oncology Group of Australia (MOGA), Pharmacy Guild of Australia and the Society of Hospital Pharmacists of Australia (SHPA). Medicines Australia was consulted and although supportive of measures that promote quality and safe use of medicines, did not receive sufficient member response to enable endorsement. The Haematology Society of Australia &New Zealand (HSANZ) have reviewed and provided support for the guidelines including distribution and reference within the organisation. The Australian Nursing and Midwifery Federation (ANMF) appraised the guidelines but were unable to provide endorsement. The Australian Government Department of Health, Department of Health Victoria and WorkSafe Victoria were provided copies of draft and final guidelines throughout their development.

2. Evidence and Recommendations

2.1. Recommendation I – Occupational health and safety risk

Recommendation	Grade	Evidence in Section
That the occupational health and safety risk to healthcare personnel handling MABs is dependent on the following risk factors:		
i. Internal Exposure Risk		
via dermal absorption	GPP	2.1.1
via inhalation absorption	GPP	2.1.2
via mucosal absorption	GPP	2.1.3
via oral absorption	IV-D	2.1.4
ii. Toxicity		
cytotoxicity	GPP	2.1.5
carcinogenicity	II-C	2.1.6
genotoxicity or mutagenicity	GPP	2.1.7
teratogenicity or developmental toxicities	IV-D	2.1.8
organ toxicity at low doses	GPP	2.1.9
immunogenicity	III-D	2.1.10

The occupational health and safety risks to healthcare personnel who handle MABs were assessed according to the risk of internalisation and evidence of toxicity of these molecules. In the setting of occupational exposure where toxicity is limited by internalisation, strong evidence of (no) internalisation was given greater weighting than weak evidence of toxicity. Criteria for toxicity was adapted from hazardous substance criteria defined by the Australian National Occupational Health and Safety Commission (NOHSC) (now Safe Work Australia) and the US National Institute for Occupational Safety and Health (NIOSH) for hazardous chemicals,[6,7] with the addition of immunogenicity (specific concern of MABs and other immunomodulatory agents) and cytotoxicity (applicable as MABs are commonly treated as cytotoxic agents).

i. Internal Exposure Risk

2.1.1. Dermal Absorption

MABs are large proteinaceous molecules. Evaluated MABs ranged in molecular size from 147-153 kilo Daltons (Appendix I). This molecular size is orders of magnitude greater than pharmaceutical agents used for topical or transdermal drug delivery and of known contact allergens which are typically less than 500 Daltons.[14] Dermal absorption of MABs is thus generally considered to be unlikely.[15-17] There are no reports listed in the literature of individual MABs causing skin irritation. However, for personnel with damaged skin, the risk of dermal absorption, local irritation or allergic reaction may still exist. Contact allergies may be triggered by excipients such as tensides (Polysorbate, (also known as Tween 20 & Tween 80)) used in various drug formulations including numerous MAB formulations. Contact allergies and non-immunological anaphylactoid reactions from non-MAB drug formulations have been reported in the literature.[18-20]

Implications for recommendation

The WG did not consider dermal absorption to be a viable mechanism of internalisation during any phase of preparation of doses for administration or administration. This recommendation is applicable for all current MABs and for newly developed MABs with similar physiochemical properties (i.e. similar molecular size, permeability) and absorption profiles. The WG considered the risk of contact allergy to be no different to other pharmaceutical products containing commonly used excipients such as tensides (GPP).

2.1.2. Absorption following inhalation

Local and systemic absorption of MABs via inhalation of aerosolised formulations has been demonstrated in animal models. However the likelihood of producing an aerosol with the required physical characteristics in the healthcare setting is limited. This view is shared by authors of an unpublished study cited by the BioPharma Environmental Health and Safety (EHS) Group in response to the NIOSH 2007 hazardous drug notice. Authors postulated that only inhalation of powdered MAB formulations would be capable of reaching the alveoli, no liquid aerosol capable of reaching the alveoli could be created under accidental conditions in the workplace, and that inhalation of liquid droplets would not be expected to extend further than the tracheobronchial tree.[17]

The structural integrity and potency of MABs are unlikely to be affected by nebulisation.[21,22] In the biophysical and functional evaluation of CA652.g2 (generated by mesh nebulisation), there was no evidence of particulate formation, no detectable degradation of the molecule and no formation of high- or low- molecular weight fragments. Furthermore, there was no change in post-nebulisation potency as measured with cell-based assay.[22]

Aerosolised cetuximab administered to genetically modified (Babl/c nude) mice demonstrated that drug accumulated durably in the lungs and passed into systemic circulation, albeit poorly and slowly.[23] An unpublished animal study quoted in the previously cited EHS correspondence provides estimated systemic absorption levels based on molecular weight of MABs.[24] Results however are of limited value with no methodological detail or sensitivity analyses provided. The study concluded that for MABs with molecular weight greater than 120 Kilo Dalton, the expected systemic absorption through inhalation is less than 5%. A range of 4-11% bioavailability at 5.7 Kilo Dalton was demonstrated at separate points.

Implications for recommendation

The WG considered that in the preparation of doses for administration (not during administration) staff may be exposed to powdered or aerosolised liquid particles. Inhalation of aerosolised MABs was considered to be a potentially viable route of internalisation with unquantified and indeterminate effects (GPP).

2.1.3. Mucosal Absorption

Local and systemic absorption of MABs has been demonstrated in animal models. In a mouse model, different MAB preparations (including IgG and IgM MABs) were administered via polymer vaginal rings designed to provide continuous antibody delivery.[25] Measured antibody concentrations remained high in the vaginal secretions for up to 30 days after

vaginal ring insertion with approximately 100 times lower concentrations in the blood and other tissues.

Mucosal absorption via intranasal drug administration has been demonstrated in porcine and mouse studies.[26,27] The administration of bevacizumab through porcine nasal mucosa demonstrated significant transmembrane absorption despite large molecular weight (149 kDa) and unfavourable physiochemical properties (marked hydrophilia). Drug assay recovered 83% of the original dose; 53% at the mucosal surface, 19% into and 11% through the mucosa. There was no evidence of any noticeable histological effects.[26] Intranasal delivery of IgA and IgG antibodies of similar molecular size to available human therapeutic MABs (molecular weight 160kDa) in mice demonstrated a rapid rise and high levels of both IgA and IgG antibodies in lung lavage, no passive transfer to the bile and no detectable serum levels.[27]

In a rat model, drops of liposome-incorporated and free MABs (murine derived IgG1 anti CD4) were topically applied (9micrograms 5 times daily for 10 days) to rat cornea to investigate impact as anti-corneal allograft rejection treatment.[28] Transplant rejection rates in liposome-formulated MAB treated rats, free MAB treated rats and untreated rats were 25%, 58% and 63% respectively. Flow cytometry analysis revealed no systemic depletion of targeted lymphocytes, indicating lack of systemic absorption. The authors concluded that the beneficial effect was likely attributable to the liposomal delivery mechanism enhancing intraocular delivery at very low doses (<50micrograms/day).

Implications for recommendation

The WG considered that in the preparation of doses for administration (not during administration) staff may be exposed to powdered or aerosolised liquid particles presenting the greatest risk of mucosal absorption via the nasal mucosal surface. Absorption of MABs via the nasal mucosal surface was considered to be a potentially viable route of internalisation with unquantified and indeterminate effects. Absorption via other mucosal surfaces was considered less likely (GPP).

2.1.4. Oral Absorption

The proteinaceous nature of MABs is thought to render molecules labile to gastric acids and enzymes, resulting in denaturation (i.e. making the MAB ineffective or inert). The expected lack of toxicity and bioavailability following oral ingestion is stated clearly in the MSDS of several evaluated MABs, including: alemtuzumab, bevacizumab and ofatumumab.[29-31]

Findings from animal[32] and human studies[33,34] however, raise doubt about these assumptions. Orally administered antibody has been demonstrated to induce a local immunologic response, inducing regulatory T cells with systemic activity.[32] CD3-specific antibody was administered to mice once daily for five days (50 – 500micrograms/dose) via oral or intravenous (IV) administration. After oral administration CD3-specific antibody appeared in the epithelium within 30 minutes and increased at 1 hour and 3 hours after administration. The orally administered agent demonstrated biological activity in the gut without modulation or depletion of T cells as seen with IV administration. The oral formulation demonstrated the same effectiveness as the IV formulation against autoimmune encephalomyelitis in mice. The Fc portion of the antibody was not required for activity with

similar effects observed with oral Fab fragments. This finding is supported by *in vivo* (human) and *in vitro* (using human gastric aspirates) studies demonstrating that although some denaturation is observed, MABs are able to survive gastric enzyme and acidic environments to retain biological activity.[33,34] This was achieved (in the human study) with co-administration of the immunoglobulin concentrate with an antacid to protect against gastric acid degradation.[34] Reduction in MAB titre following gastric digestion was attributable to acidic conditions rather than proteolytic cleavage by pepsin.[33] The denaturation of IgG has been studied under different environmental conditions including heat and pH transitions. The Fc and Fab fragments were found to have different sensitivities with Fab most sensitive to heat (Fab denaturation at 55-60C vs. 60-75C for Fc) and Fc to decreasing pH (Fc denaturation at pH3.5 vs. ph2.0 for Fab).[35]

Implications for recommendation

The WG considered that oral exposure to MABs may occur in the workplace setting, with hand to mouth contamination being the most likely scenario. Although absorption of ingested MABs was considered to be a potentially viable route of internalisation with unquantified and indeterminate effects (IV-D), occupational exposure at levels required for systemic bioavailability was considered highly unlikely.

ii. Toxicity

2.1.5. Cytotoxicity

No MAB unless conjugated to a cytotoxic agent has direct cytotoxic activity and there is no evidence or known biological mechanism for the direct cytotoxic potential of MABs. MABs can however exhibit immune-mediated cytotoxicity with antibody-dependent cellular cytotoxicity (ADCC) being a major mechanism of action.[5,36]

An in vivo (mice) study of zalutumumab (investigational therapeutic epidermal growth factor receptor specific MAB) demonstrated the importance of ADCC induction for therapeutic efficacy.[36] ADCC (as the only mode of action) was capable of reducing tumour growth at low MAB concentrations (5mg/kg). The role of ADCC alone was found to be ineffective for controlling established tumours of large volume where EGFR signalling inhibition is required.

Other in vitro studies have suggested an alternative mechanism of cytotoxicity for MABs. Certolizumab Pegol exhibits cytotoxic activity by directly inducing the death of non-apoptotic cells in transmembrane TNF-α expressing cells. Certolizumab is the likely cause of this as Pegol (a polyethylene glycol) is non-toxic and unlikely to elicit any cytotoxic effect.[37]

Implications for recommendation

The WG considered MABs capable of inflicting immune-mediated cytotoxicity at therapeutic doses with unquantified and indeterminate effects at long term low dose exposure levels (GPP). The WG's opinion is that immune-mediated cytotoxicity is explicitly different to the direct cytotoxic action of traditional anticancer agents and that MAB admixtures should not be labelled as 'cytotoxic' or 'treat as cytotoxic', unless there is evidence to the contrary.

2.1.6. Carcinogenicity

MABs are not required to be evaluated for carcinogenicity.[8] Despite this, there is an association between some MABs and increased risk of lymphoma and other malignancies during therapeutic use. Four MABs (infliximab, adalimumab, certolizumab and golimumab) have a boxed warning for "lymphoma and other malignancies", which is a class warning applying to all tumour necrosis factor (TNF) blockers. No evidence of carcinogenicity has been identified for commonly used cancer MABs (trastuzumab, bevacizumab, cetuximab, panitumumab, alemtuzumab, gemtuzumab or rituximab).

Table 3 - Carcinogenicity of Monoclonal Antibodies at therapeutic doses

MAB	Carcinogenicity *at therapeutic exposures
Adalimumab[38]	Black Box Warning - Malignancies more often than in controls, lymphoma more often than in general population
Infliximab[38]	Black Box Warning - Rare post-marketing cases hepatic t-cell lymphoma *all with concurrent azathioprine or 6-mercaptopurine
Certolizumab[39]	Black Box Warning - Malignant neoplasms in 0.4% patients (short term data only)*all with concurrent methotrexate
Golimumab[40]	Black Box Warning - Malignant neoplasms observed in no greater than 3% patients *diversity in types of cancers, all with concurrent methotrexate, sulfasalazine or hydroxychloroquine
Omalizumab[38]	Product Information Warning - Malignant neoplasms observed in 0.5% patients vs. 0.2% in control patients*diversity in type of cancers, short duration of omalizumab exposure and clinical features of individual cases render causal relationship unlikely
Muromonab[38]	Product Information Warning - Association between lymphoproliferative disorders (benign polyclonal B cell hyperplasia, malignant and often fatal monoclonal B cell lymphomas) in paediatric liver allograft recipients

Implications for recommendation

The WG considered that some MABs are potentially carcinogenic at therapeutic doses with unquantified and indeterminate effects at long term low dose exposure levels (II-C).

2.1.7. Genotoxicity/ Mutagenicity

MABs are not required to be evaluated for genotoxicity.[8] However according to a safety and immunotoxicity assessments, immunomodulatory MABs do not interact directly with DNA (hence not directly genotoxic).[41] This view point is agreed upon by the American College of Toxicology (ACT) and German Society of Toxicology who state that there is little to no concern that bio-therapeutics may induce a genotoxic insult.[42]

Implications for recommendation

The WG considered MABs to be neither genotoxic nor mutagenic (GPP).

2.1.8. Teratogenicity or other developmental toxicity

There is no evidence of teratogenicity or other developmental toxicity associated with occupational exposure to MABs. However a biological mechanism for MAB-induced teratogenicity has been demonstrated at therapeutic doses.

Table 4 - Teratogenicity of monoclonal antibodies at therapeutic doses

MAB	Teratogenicity or other developmental toxicity	Evidence
Alemtuzumab	No data, potential pharmacological mechanism	Ph
Bevacizumab	Teratogenic and embryotoxic	An
Brentuximab-Vedotin	Decreased embryo viability and foetal malformations	An
Cetuximab	Increased incidence of abortion	An
Denosumab	Impaired bone growth and eruption of dentition. Foetal loss, stillbirths, postnatal mortality, and histological changes in infants.	An
Ipilimumab	Abortion, stillbirth, premature delivery and infant mortality.	An
Ofatumumab	Lower foetal spleen weights and depleted B cells.	An
Panitumumab	Foetal abortions or deaths at all dose levels tested.	An
Rituximab	Transient B-cell depletion and lymphocytopenia in infants born to mothers exposed to rituximab. Spontaneous abortion with rituximab and methotrexate.	Hu
	B-cell depletion shown in the foetus. No evidence of embryotoxicity.	An
Trastuzumab	Foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus	Hu
	No evidence of harm to the foetus	An
Trastuzumab-Emtansine	Emtansine is a cytotoxic microtubule inhibitor and has potential to cause embryotoxicity and teratogenicity. Trastuzumab effects as above.	Ph

An: animal studies, Hu: human studies or case reports, Ph: pharmacological principles. Refer to appendix I for citations; manufacturer material safety data sheets and product information sheets.

Implications for recommendation

The WG considered that some MABs are teratogenic at therapeutic doses with unquantified and indeterminate effects at long term low dose exposure levels (IV-D)*.

*Grading based on highest level of evidence for MABs with clinical evidence (trastuzumab and rituximab)

2.1.9. Organ toxicity at low doses

There is no evidence of organ toxicity from sub-therapeutic doses or from systemic exposure (bioavailability) that may be plausibly achieved through continuous occupational exposure, though safe dose limits and thresholds have not been defined. Several guidelines extrapolate toxicity profiles from therapeutic doses[15,43,44] which may be misleading considering evidence relating to (lack of) potential exposure routes. (see 2.1.1-2.1.4) suggests that the risk and extent of internalisation through occupational exposure is small. However, this must be balanced with the risk of continuous exposure and drug accumulation, since MABs generally have longer elimination half-lives (18 hours to 26 days)[4] compared to small molecules notwithstanding disease- and drug- related factors that influence drug clearance.

Implications for recommendation

The WG considered that there is no evidence for organ toxicity at exposure to low doses of MABs (GPP).

2.1.10. Immunogenicity

There is no data for immunogenicity associated with occupational exposure to MABs. A biological mechanism for MAB-induced immunogenicity is plausible and has been demonstrated with infliximab.

The immunogenicity of infliximab was investigated in a prospective cohort study of 125 patients.[45] Patients treated with infliximab developed anti-drug-antibodies which was associated with an increased risk of infusion reactions (anti-infliximab-antibodies >8.0µg/mL vs. <8.0µg/mL, Relative Risk = 2.40, 95%CI 1.65-3.66, p<0.001). Infusion reactions were not characterised as allergic or non-allergic in nature. Concomitant immunosuppressive therapy was predictive of low titres of anti-infliximab antibodies (p<0.001) and high concentrations of infliximab four weeks after an infusion (p<0.001). There is no evidence for systemic absorption in the context of handling or accidental spillage of infliximab or other anti-tumour necrosis factor alpha MABs.[46]

Pooled results from 81 studies reporting immunogenicity in patients treated with MABs found that levels of anti-antibody response were greatest for murine then chimeric then humanised MABs.[47] The incidence of anti-antibody response (AAR) was defined by the authors as negligible (<2% of patients), tolerable (2-15% of patients) or marked (>15% of patients). All studies that reported anti-antibody response were included in the review regardless of size or design on the basis that there is no scientifically valid evaluation or reporting method for immunogenicity. Accordingly, results were taken as reported without further interpretation. The study included 44 murine MAB studies, 15 chimeric MAB studies and 22 humanized MAB studies. The AAR for murine MABs developing Human Anti-Mouse Antibodies (HAMA) was marked (84%) and tolerable (7%). For chimeric MABs developing Human Anti Chimeric Antibodies (HACA) it was marked (40%) and tolerable (27%). For humanised MABs Human Anti-Human Antibodies (HAHA) it was marked (9%) and tolerable (36%). AAR was less in B- cell targeted (34%) than non B-cell targeted MABs (75%).

Implications for recommendation

The WG considered that immunogenicity may occur at therapeutic exposures with unquantified and indeterminate effects at long term low dose exposure levels (III-D).

2.2. Recommendation II – Safe Handling Procedures

Recommendation	Grade	Evidence in Section
From an occupational health and safety perspective, it would be prudent for MABs to require greater handling precautions than other non-hazardous injectable medications however they do not warrant full cytotoxic precautions, with exceptions only where sufficient evidence exists of safety concerns for a specific MAB.	GPP	2.2.1

2.2.1. Safe Handling Procedures

Safe handling procedures are recommended to mitigate potential occupational health and safety risks (see section 2.1).

Whilst data does not exist for all MABs and whilst individual MABs have different molecular targets and toxicity profiles (at therapeutic doses), all MABs evaluated possess similar molecular properties and were thus considered to have similar risk of internalisation. This was considered to be the fundamental process for assessing occupational exposure risk and the rationale behind recommending class rather than agent specific handling procedures. Only where sufficient evidence exists for an individual MAB should handling procedures differ from class recommendations. Refer to appendix 1 for a comparison of drug properties in select commercially available MABs.

Implications for recommendation

The WG considered that although toxicity profiles may vary, all currently available MABs have a similar low risk of internalisation with occupational exposure levels. Safe handling recommendations within this guideline are therefore applicable to all MABs (class effect). Future development of MABs with differing physiochemical properties (i.e. smaller molecular size) or with formulations demonstrated to alter absorption and/or permeability (i.e. optimised vehicle) should be re-assessed according to risk factors identified in recommendation 1 of these guidelines (GPP).

2.3. Recommendation III – Stratification of Exposure Risk

Recommendation	Grade	Evidence in Section
Safe handling procedures should be stratified according to:		
i. Healthcare staff role (preparation, administration, transportation/disposal)	III-D	2.3.1
ii. Health considerations (e.g. pregnancy)	GPP	2.3.2

2.3.1. Healthcare staff role

The source of occupational exposure and opportunities for internalisation of MABs vary depending on the role and activities undertaken by personnel. Exposure to all formulations (powder, liquid or lyophilised products), carries a theoretical risk of internalisation in the workplace setting via mucosal, inhalation and oral routes (see section 2.1 for a specific discussion of MABs). Staff involved in the preparation of doses for administration may be exposed to powdered or aerosolised liquid particles with a potential risk of inhalation. Liquid drug exposure, both in the manufacturing process and via contamination within other workspaces may result in internalisation via mucosal and oral (hand to mouth) routes.

In a multicentre study measuring healthcare personnel glove contamination with cytotoxics, staff were found to have differing levels of contamination depending on their role.[48] Pharmacy technicians had the greatest level of exposure followed by oncology nurses then cleaning personnel. Tasks yielding the highest proportion of contaminated samples were drug preparation (36%), patient washing (23%), decanting urine (17%), changing bed linen (6%) and toilet cleaning (6%). An Australian group looked at cyclophosphamide contamination in various locations of the manufacturing (cytotoxic down flow) cabinet, anteroom and product checking area in 10 different hospital pharmacies.[49] The level of exposure noted for areas of the anteroom used in preparation (e.g. areas in the cabinet, work area in the anteroom) ranged from nil detected to 11.71ng/cm^2. Levels of exposure in checking area ranged from nil detected to 0.67ng/cm^2. Although similar studies have not been conducted for MABs, similar levels of surface contamination may be expected. The significance of MAB surface contamination is unknown.

Implications for recommendation

The WG considered that healthcare professionals involved in the preparation of doses for administration have the highest risk of occupational exposure (III-D).

2.3.2. Health Considerations

There is no evidence regarding teratogenicity resulting from occupational exposure to MABs. In the event of occupational exposure and subsequent internalisation, it is possible that a pregnant woman may be at risk of teratogenic effects that have been observed at therapeutic doses. Manufacturer handling recommendations for pregnant personnel are summarised in table 5. Given that MABs exert their effect via the immune system, it is conceivable that in the event of occupational exposure and subsequent internalisation, personnel with compromised immune function may be more susceptible to immune mediated effects.

Table 5 - Manufacturer handling recommendations for pregnant personnel

Drug	Handling Recommendations	Formulation
Alemtuzumab	Avoid if pregnant or planning pregnancy	Solution
Bevacizumab*, Cetuximab*, Denosumab*, Ipilimumab*, Ofatumumab*, Panitumumab*, Rituximab*	No information available	Solution
Trastuzumab*	No information available	Powder
Brentuximab Vedotin*, Trastuzumab-Emtansine*	As per procedures for anticancer drugs	Powder

*Teratogenic or developmental toxicities at therapeutic (or higher) doses in animal or human studies. Refer to appendix I for citations; manufacturer material safety data sheets and product information sheets.

Implications for recommendation

The WG considered that without evidence to demonstrate safety, healthcare personnel with relevant health considerations (pregnancy, immunosuppression or other) should avoid the preparation of doses for administration, where exposure risk is the greatest (GPP).

2.4. Recommendation IV – Waste Management

Recommendation	Grade	Evidence in Section
Procedures for the handling of waste products generated during the preparation or clinical use of MABs are as follows:		
i. Waste products generated during the preparation of MABs, should be disposed as per standard operating procedures for parenterally administered agents, i.e. not classified as cytotoxic waste	GPP	2.4.1
ii. Waste products and/or bodily fluids of patients who have been administered MABs should be disposed as per standard operating procedures for parenterally administered agents, i.e. not classified as cytotoxic waste	GPP	2.4.2
The above recommendations exclude MABs conjugated to cytotoxic or radioactive compounds, which should be handled according to relevant procedures for cytotoxic and radioactive agents (refer to section 5		

2.4.1. Manufacturing waste and spills

MABs do not have direct cytotoxic activity and no known or potential mechanism of internalisation via dermal contact, the most likely form of contact when cleaning or disposing of contaminated waste products. The stability of MABs - large fragile proteinaceous molecules - in unprotected environments (i.e. open benches or waste bins) is untested; theoretically, their ability to withstand physical, temperature and pH variation is unlikely.

Implications for recommendation

The WG considered that exposure to waste products does not present an occupational health and safety risk to healthcare personnel beyond that of other parenterally administered agents (GPP).

2.4.2. Patient waste and bodily fluids

The likelihood that active and/or toxic metabolites are present in patient waste is highly improbable. The proteinaceous nature of MABs renders them liable to digestion and breakdown prior to elimination. Furthermore, the targeted action and durable effects of MABs correspond to retention in the body for weeks after administration. Elimination half- lives range from 3.9 to 11.1 days for panitumumab and 6 to 52 days for rituximab.[50,51] Excluding MABs conjugated to cytotoxic, radioactive or other hazardous substances, the risk of bioconversion to toxic metabolites is perceived to be low.[52]

Implications for recommendation

The WG considered that exposure to patient waste products and/or bodily fluids does not present an occupational health and safety risk to healthcare personnel (GPP).

2.5. Recommendation V – Available Safety Interventions

Recommendation	Grade	Evidence in Section
The range of available interventions / safeguards to minimise occupational exposure are:		
i. Personal Protective Equipment (PPE)		2.5.1
Gloves	III-D	2.5.1.1
Gown	GPP	2.5.1.2
Respirator mask	GPP	2.5.1.3
Protective eyewear	GPP	2.5.1.4
ii. Discipline based aseptic technique	III-D	2.5.2
iii. Isolator Cabinet	GPP	2.5.3
iv. Cytotoxic Drug Safety Cabinet (CTDSC)	GPP	2.5.4
v. Closed System Drug Transfer Devices (CSDTD)	III-D	2.5.5
And use of these should be risk stratified according to risk of internal exposure and toxicity		

2.5.1. Personnel Protective Equipment (PPE)

2.5.1.1. Gloves

Gloves are worn to prevent dermal absorption and/or skin irritation via the hands. A Dutch study measured actual hand exposure to cyclophosphamide of pharmacy technicians who prepared the drug wearing 2 pairs of latex surgical gloves.[48] The amount of cyclophosphamide on the gloves (a measure of potential exposure) and on the hands (measure of glove effectiveness) were reported. While the gloves contained a median of
0.45 ng/cm2/min cyclophosphamide, hand wash samples contained 0.002 ng/cm2/min; the use of gloves reduced exposure by 98.5%; p= 0.009.

Implications for recommendation

The WG considered that use of gloves are not warranted for either the preparation of doses for administration or handling of MABs from an occupational exposure perspective due to the lack of dermal penetration (III-D). They may, however, be considered as part of good aseptic technique.[53]

2.5.1.2. Gowns

Gowns provide splash protection and prevent dermal contact with hazardous substances. Gowns with polyethylene or vinyl coating have been shown to be superior to polypropylene homopolymer gowns which failed splash testing, allowing penetration of both water and non- water based cytotoxic agents.[54] Australian cytotoxic handling guidelines recommend an impervious material and advocate for the use of coveralls over gowns.[55] The guidelines cite a study which describes Saranex-laminated or polyethylene-coated Tyvek as the most protective barrier garments.[56] These garments were most protective against evaluated chemotherapy agents. It is not known whether such protection is needed for MABs as they are considerably larger molecules, with unknown level of garment penetration, poor membrane permeability and no known mechanism of dermal absorption.[14,15,17]

Implications for recommendation

The WG considered that use of gowns and/or coveralls are not warranted for either the preparation of doses for administration or handling of MABs due to the lack of dermal penetration of MABs (GPP).

2.5.1.3. Respirator Mask

Respirator masks prevent against inhalation and mucosal (nasal) absorption. Australian and New Zealand standards for the selection, use, maintenance and performance of respiratory protective equipment should be followed where use of a respirator is indicated; AS/NZS 1715:2009 and AS/NZS 1716:2012.[57,58] Respiratory protection is indicated for the handling of cytotoxic agents.[10,55] P2 (N95) masks filter 94% of sodium chloride particles (which are approximately 58.5 Daltons in size).[59] MABs are substantially larger molecules when compared with sodium chloride (>140 kilo Daltons), suggesting that these masks would offer adequate protection.

Implications for recommendation

The WG considered that respirator mask should be worn during the preparation of doses for administration, where the risk of splashing and aerosolisation is greatest, to prevent mucosal (nasal) and inhalation exposure. Respirator masks are not mandated during the administration of MABs however may be considered during the administration of intravenous formulations where the dis/connecting administration lines may present a risk of aerosolisation, particularly with new or inexperienced staff (GPP).

2.5.1.4. Protective eyewear

Protective eyewear acts to prevent ocular irritation and absorption. Ocular absorption of MABs has been demonstrated in animal studies.[28] Eyewear with side shields afford total protection from splashes as the entire periphery of the goggle is in contact with the face.[60] The use of glasses with side-shields is recommended in Australian cytotoxic handling guidelines.[61]

Implications for recommendation

The WG considered that protective eyewear should be worn during the preparation of doses for administration, where the risk of splashing is greatest, to prevent mucosal (ocular) exposure. Protective eyewear is not mandated during the administration of MABs however may be considered during the administration of intravenous formulations where the dis/connecting administration lines may present a risk of aerosolisation, particularly with new or inexperienced staff (GPP).

2.5.2. Discipline based aseptic technique

According to the Australian Commission on Safety and Quality in Healthcare, aseptic technique aims to prevent pathogenic organisms, in sufficient quantities to cause infection, from being introduced to susceptible sites by hands, surfaces and equipment.[53] It is important to differentiate aseptic technique, which can be achieved in any hospital or community setting, from sterile technique, which can only be achieved in controlled environments such as a laminar flow cabinet or specially equipped theatre.

Aseptic technique has been widely studied in relation to microbial contamination of parenteral products however not with consideration of occupational exposure. A study compared levels of microbial contamination in parenteral medications prepared either on the ward by nurses or by pharmacy operators (not known if a pharmacist or pharmacy technician).[62] Both syringe and surface contamination were

significantly lower with pharmacy operators than for nursing staff with a 6.9% reduction in syringe contamination and 70% reduction in surface contamination. The authors concluded that the training and aseptic technique experience of the pharmacy operators was the likely reason for the reduced contamination rates. A two-year series study evaluating 539 applications of aseptic technique found a 4.4% and 6.2% microbial contamination rate among pharmacists and technicians respectively.[63] Another study designed to compare microbial contamination in different types of pharmacy cleanrooms failed to identify a difference between clean room type, did however identify significant differences in contamination rates between pharmacists (2/2057) and technicians (11/2000), p=0.012.[64] The authors concluded that the most important determinant of microbial contamination was operator aseptic technique, not the compounding environment.

Implications for recommendation

The WG considered that aseptic technique, as defined by the Australian Commission on Safety and Quality in Healthcare,[53] should be implemented for the preparation of doses for administration, as per any other injectable medicines (III-D).

2.5.3. Isolator Cabinet

An isolator cabinet (also known as a pharmaceutical isolator cabinet) is a device that separates a pharmaceutical process from the operator and surrounding environments, thereby protecting the operator from the hazardous material being handled. An isolator cabinet should conform to Australian Standards (AS4273)[65] and comprises of four main elements: controlled workspace (created due to the separative nature of the cabinet), transfer device/s (such as a door which the operator can open in order to transfer materials into the work zone), access device (the means by which the activity is carried out – many cabinets have inbuilt gloves which the operator uses to carry out the relevant activity) and decontamination system (they must be able to be easily cleaned and decontaminated). Isolator cabinets can be used to prepare cytotoxic drugs however they must provide an equivalent level of protection to the operator, environment and product as cytotoxic drug safety cabinets, and meet Australian standards (AS2567).[66] These cabinets only offer full protection when in optimal working condition, with the Australian Standard providing a recommended testing schedule (for gloves, leak and microbial tests). Although they are stand-alone units, they must be located in their own dedicated room.[55]

Implications for recommendation

The WG considered that the use of isolator cabinets is not required for the preparation of doses for administration (GPP).

2.5.4. Cytotoxic Drug Safety Cabinets

The Australian Standard for laminar flow cytotoxic drug safety cabinets (CDSCs) specifies requirements for laminar flow cytotoxic drug safety containment cabinets (AS 2567).[66] These are intended to provide protection for personnel, the environment, and cytotoxic drug products. However they may also find wider application for handling other hazardous drugs and materials. CDSCs are primarily designed to contain aerosols, and are not intended to provide complete protection against particles which may be ejected during procedures such as tablet crushing and grinding. CDSCs afford both protection to the operator from hazardous and cytotoxic substances and to materials being manipulated from biological and other contamination. The down-flow cabinet has laminar air flow from the top to the base of the cabinet. There is a glass barrier at the front of the cabinet and a full width grill in which both laminar flow air formed within the cabinet and outside room air is drawn in to create an air-curtain through which the

operator works. Laminar flow air is unable to leave the cabinet and contaminate the operator.

Implications for recommendation

The WG considered that the use of cytotoxic drug safety cabinets (CDSCs) are not required for the preparation of doses for administration (GPP).

2.5.5. Closed System Drug Transfer Device

Closed system drug transfer devices (CSDTDs) are a means to provide protection from exposure to hazardous and cytotoxic substances in addition to personal protective equipment and cytotoxic drug safety cabinets. NIOSH define CSDTD as being "a device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system".[67] Both the International Society of Oncology Pharmacy Practitioners (ISOPP) and the American Society of Health-System Pharmacists (ASHP) endorse this definition.[10,68] ISOPP highlights the requirement of CSDTDs to prevent against both microbiological (product) and chemical (environmental) contamination, strongly recommending the terminology of Containment Device (described as leak-proof and airtight) for devices providing protection against chemical contamination.[10]

Currently, there are no Australian standards for specifications of CSDTDs. The Society of Hospital Pharmacists of Australia (SHPA) recommends the use of CSDTDs to minimise cross-contamination when handling hazardous substances, however does not provide a definition of an acceptable CSDTD.[69]

Evaluation of different brands of CSDTDs found differing levels of contamination among commercially available devices tested by two independent research groups.[70,71] In both studies, PhaSeal® was the only brand meeting NIOSH and ISOPP definitions; closed system (in reference to both microbiological and chemical contamination) and containment of drug throughout all preparation and administration manipulations. A microbial contamination study of the PhaSeal® CSDTD reported a contamination rate of 1.8% among 332 tested samples, 99%CI 0.05% to 3.6%, $p<0.001$.[72] Evaluation of PhaSeal® in Australian conditions demonstrated a 68% reduction in chemical contamination (total contamination of tested surfaces) 12 months after implementation of the device.[73] Several international studies report similar findings, consistently demonstrating significant reductions in surface and operator contamination (cytotoxic drugs) when using CSDTD compared with standard preparation techniques.[74-76]

Implications for recommendation

The WG considered that the use of closed system drug transfer devices (CSDTDs) are not required for the preparation of doses for administration, although acknowledge that they can reduce operator exposure and product contamination (III-D).

2.6. Recommendation VI – Operational and Clinical Factors

Recommendation		Grade	Evidence in Section
That the following factors (not related to occupational exposure risk) should be considered when determining preparation and handling recommendations			
i.	Vial Sharing	GPP	2.6.1
ii.	Complexity of preparation	GPP	2.6.2
iii.	Medication Error	GPP	2.6.3

2.6.1. Vial Sharing

According to manufacturer product information sheets MABs are intended for use as single use-vials. Vial sharing in this context therefore differs from multi-dose vials where the intention is that each vial contains more than one dose of medication, where vials typically contain an antimicrobial preservative to help prevent the growth of bacteria, and where manufacturer labelling clearly identifies the product as a multi-use vial.[77] The Australian Guidelines for the Prevention and Control of Infection in Healthcare state that multi-dose vials should not be used except where they are intended solely for the exclusive use of an individual patient (e.g. insulin).[53] The US Centres for Disease Control and Prevention (CDC) advocates that multi-dose vials should be dedicated to a single patient whenever possible however can be used for more than one patient providing they are not stored or accessed in the immediate patient treatment area.[77] Recommendations from the UK National Health System (NHS) are such that injectable medicines be treated as intended for single use only unless specified otherwise within manufacturer labelling and licencing conditions.[78] The World Health Organisation advocates against the use multi-dose vials wherever possible.[79]

Anecdotal evidence from individual institution procedures suggest that only when compounding occurs in a pharmacy is it appropriate to vial share. Guidelines such as SHPA standards for safe handling of cytotoxics recommend that opened or used vials should not be left in the cytotoxic drug safety cabinet for later use.[55] Anecdotally vial sharing is common practice, particularly at larger hospitals and healthcare services where compounding occurs in a pharmacy. Revised funding arrangements under the Pharmaceutical Benefits Scheme (PBS) are such that chemotherapy drugs costs are reimbursed based on using the most efficient combination of available vial strengths to achieve a given dose.[80] In some circumstances this may result in residual volume and may influence a preference toward vial sharing. This is a particularly important consideration given the high cost of MABs and high likelihood that a preparation of a given dose will result in production of part vials (table 6).

Vial sharing outside of controlled environments, without trained staff using aseptic preparation techniques, increases the risk of contamination. A study of 227 multi-dose vials across a 1300-bed hospital demonstrated a contamination rate (primarily involving *Staphylococcus epidermidis*) of 0.9% (95% CI, 0.3-2.1), a 50% compliance rate for documenting vial expiry dates and identification that 13% of vials had already expired.[81]

Implications for recommendation

The WG considered that vial-sharing, whilst not recommended by manufacturers and not endorsed by major health and safety bodies, does occur in routine clinical practice. The WG agreed that the practice of vial-sharing increases risks associated with microbial

contamination. Consensus agreement for the most appropriate location for the preparation of doses using vial-sharing was not achieved. The WG considered that the use of vial-sharing in the preparation of MABs was no different to vial-sharing for other parental medicines and advise that institutions follow local existing policy relating to this practice.

2.6.2. Complexity of preparation

As the number of preparation steps increase, so too does the opportunity for manufacturing error, occupational exposure, and/or microbial contamination. Preparation involving complex techniques and/or numerous manipulations may result in error if prepared by inexperienced staff. This is supported by evidence demonstrating reduced microbial contamination in parenteral products prepared by skilled staff.[62,64] This may be particularly relevant for smaller healthcare services where staff would not routinely handle or manufacture these agents. The risk of antimicrobial contamination is not insignificant for cancer patients who are often immunocompromised; however preparation of other parenterally administered agents (e.g. intravenous paracetamol or anti-infectives) does not command additional precautions in this population.

Most MABs require between 2 to 8 manufacturing steps, with high dose ofatumumab requiring up to 23 manipulations (table 6). Prolia® (denosumab) is the only MAB currently available in a ready-to-use formulation (pre-filled syringe), however this brand is only marketed and PBS reimbursable for the indication of osteoporosis. Xgeva® (denosumab) indicated for bone metastasis, comes as a concentrated liquid which is withdrawn into a syringe prior to administration.

Implications for recommendation

The WG considered that complexity of preparation is difficult to define and will have different implications across individual health services. Complex (i.e. gentle agitation) or multiple vial (i.e. >3 vials) preparations may be best undertaken by experienced and well trained staff. In some institutions, this may be achieved in the ward environment, whilst in other institutions this may be best achieved and monitored in a centralised manufacturing location such as a pharmacy cleanroom (GPP).

2.6.3. Medication error

Centralised dispensing or compounding often occurs for high risk (or expensive) drugs to ensure that the prescription or administration order is independently validated by a pharmacist prior to dispensing/compounding. The A-PINCH acronym used by the Clinical Excellence Commission identifies classes of medicines deemed high risk; **A**nti-infectives, **P**otassium and other electrolytes, **I**nsulin, **N**arcotics and other sedatives, **C**hemotherapeutic agents, and **H**eparins and other anticoagulants.[82] Although MABs are not considered to be traditional chemotherapy agents, when used in therapeutic doses they do result in severe side effects for some patients.

Many MABs are available in vials of multiple strengths (table 6). This could lead to accidental product selection error and inadvertent preparation and/or administration of an incorrect dose. Errors in selection may be more likely with less experienced staff.

Implications for recommendation

The WG considered that MABs, unlike chemotherapeutic agents, have a large therapeutic window and as such need not be considered within the A-PINCH 'high risk' medication list. Error (dose calculation, vial selection or other) may be less likely with experienced and well trained staff. In some institutions, this may be achieved in the ward environment, whilst in other institutions this may be best achieved and monitored in a centralised manufacturing location such as a pharmacy cleanroom (GPP).

Table 6 - Formulation, Manufacturing and Dosing Considerations

Drug Name	Cost	Formulation	Vial Size(s)	Preparation Steps	Part vials likely	Special instructions during preparation	Dosing
Alemtuzumab	$1000 ^	Solution	30mg/1ml	2	No	Invert infusion bag gently to mix solution (DO NOT SHAKE)	Fixed Dose
Bevacizumab	$3971.33 *	Solution	400mg/16ml 100mg/4ml	2	Yes	Do not shake excessively	Weight
Brentuximab Vedotin	$5400.00	Powder	50mg	6-8	Yes	Direct stream of diluent toward wall of vial (not directly at the cake or powder during reconstitution), gently swirl vial to aid dissolution (DO NOT SHAKE)	BSA
Cetuximab	$3170.33 *	Solution	500mg/100ml 100mg/20ml	2-3	Yes	None specific	BSA
Denosumab	$298.90 * (Prolia) $532.18 * (Xgeva)	Solution	60mg/1ml 120mg/1.7ml	0 (Prolia) 1 (Xgeva)	No	Do not shake excessively	Fixed Dose
Ipilimumab	$47583.82 *	Solution	50mg/10ml 200mg/40ml	2	Yes	Allow the vials to stand at room temperature for approximately 5 minutes before using.	Weight
Ofatumumab	$315.82 ^	Solution	100mg/5ml	300mg – 6 2g – 23	No	Infusion bag be inverted gently to mix solution (DO NOT SHAKE)	Fixed Dose
Panitumumab	$730 ^	Solution	100mg/5ml	2	Yes	Infusion bag be inverted gently to mix solution (DO NOT SHAKE)	Weight
Rituximab	$3723.06 *	Solution	500mg/50ml 100ml/10ml	2	Yes	Gently invert the bag to avoid foaming.	BSA
Trastuzumab	$3604.02 *	Powder	150mg 60mg	5	Yes	Direct stream of diluent into cake or powder during reconstitution, gently swirl vial to aid dissolution (DO NOT SHAKE), excessive foaming during reconstitution or shaking the reconstituted solution can result in problems with the volume that can be withdrawn.	Weight
Trastuzumab-Emtansine	$9800 /month #	Powder	100mg 160mg	5	Yes	Gently swirl vial to aid dissolution, infusion bag be inverted gently to mix solution (DO NOT SHAKE in either circumstance)	Weight

*Dispensed price per maximum amount (per Pharmaceutical Benefits Scheme (PBS) – www.pbs.gov.au), # http://www.fiercebiotech.com/story/rochegenentechs-breakthrough-t- dm1-wins-blockbuster-ok-breast-cancer/2013-02-22, ^ Per verbal communication with pharmaceutical company

2.7. Recommendation VII – Handling Recommendations

Recommendation	Grade	Evidence in Section
The following risk matrix and flow chart should be utilised when considering handling precautions for MABs. Decisions leading to these recommendations consider occupational health and safety risks as well as operational and clinical factors. Any agent lacking sufficient information to assign a risk category (such as clinical trial agents) is stipulated to be treated as high risk until additional information becomes available	GPP	2.7

2.7.1. Decision support tools

Safe handling recommendations are based on risk of internalisation and toxicity (established using risk matrix) and with due regard to operational and clinical factors (established using flow chart). Recommendations apply to the handling of MABs during the preparation of doses for administration, during administration of doses, and to the handling of waste products generated during the preparation of doses for administration and/or cleaning of spills. Prior to the implementation of any process changes as a result of recommendations within these guidelines, staff education & training and careful risk management steps should be undertaken.

1. Assign a risk category

Undertake an occupational health and safety risk assessment using risk matrix (2.7.2 – table 7). This may be completed for individual MABs where evidence exists for differing internalisation or toxicity profile or for the class as a whole where there is no evidence of differing profile. The current recommendation is that all MABs may be assessed as a class (recommendation 2).

2. Determine minimum safe handling requirements

Based on above risk category, determine recommended safe handling precautions (2.7.2 – table 8).

3. Determine location for preparation

Take assigned risk category and use the flow chart (2.7.3 – figure 1) to determine the recommended location for the preparation of doses for administration based on various clinical and operational scenarios.

2.7.2. Risk Matrix (occupational health and safety risk assessment)

Overall risk of exposure was assessed based on likelihood of exposure and risk of internalisation. Within the below risk matrix, likelihood of exposure refers to the likelihood that healthcare personnel will be exposed to MABs. As there is no known consequence of low dose occupational exposure, the consequence of exposure was determined by the risk of internalisation and was based on evidence from recommendation I.

Table 7 – Exposure Risk

Risk Matrix		Risk of internalisation			
		None	Low	Moderate	High
Likelihood of Exposure	Unlikely		Oral	Inhalation* Mucosal*	
	Possible			Inhalation** Mucosal**	
	Likely	Dermal			

*Limited to administration process

**Limited to preparation of doses for administration

Table 8 - Recommended handling precautions based on exposure risk

Exposure Risk	Recommended Handling Precaution
No / Low Risk	No additional precautions required, standard operating procedures for both the preparation of doses for administration and administration.
Moderate Risk	No additional precautions required, standard operating procedures for administration. Protective mask and eyewear, in addition to standard operating procedures for the preparation of doses for administration.
High Risk	Treat like a cytotoxic or hazardous substance for both the preparation of doses for administration and administration.

*Standard Operating Procedures: standard operating procedure for parenterally administered pharmaceutical agents (i.e. aseptic technique according to the Australian Commission on Safety and Quality in Healthcare[53]).

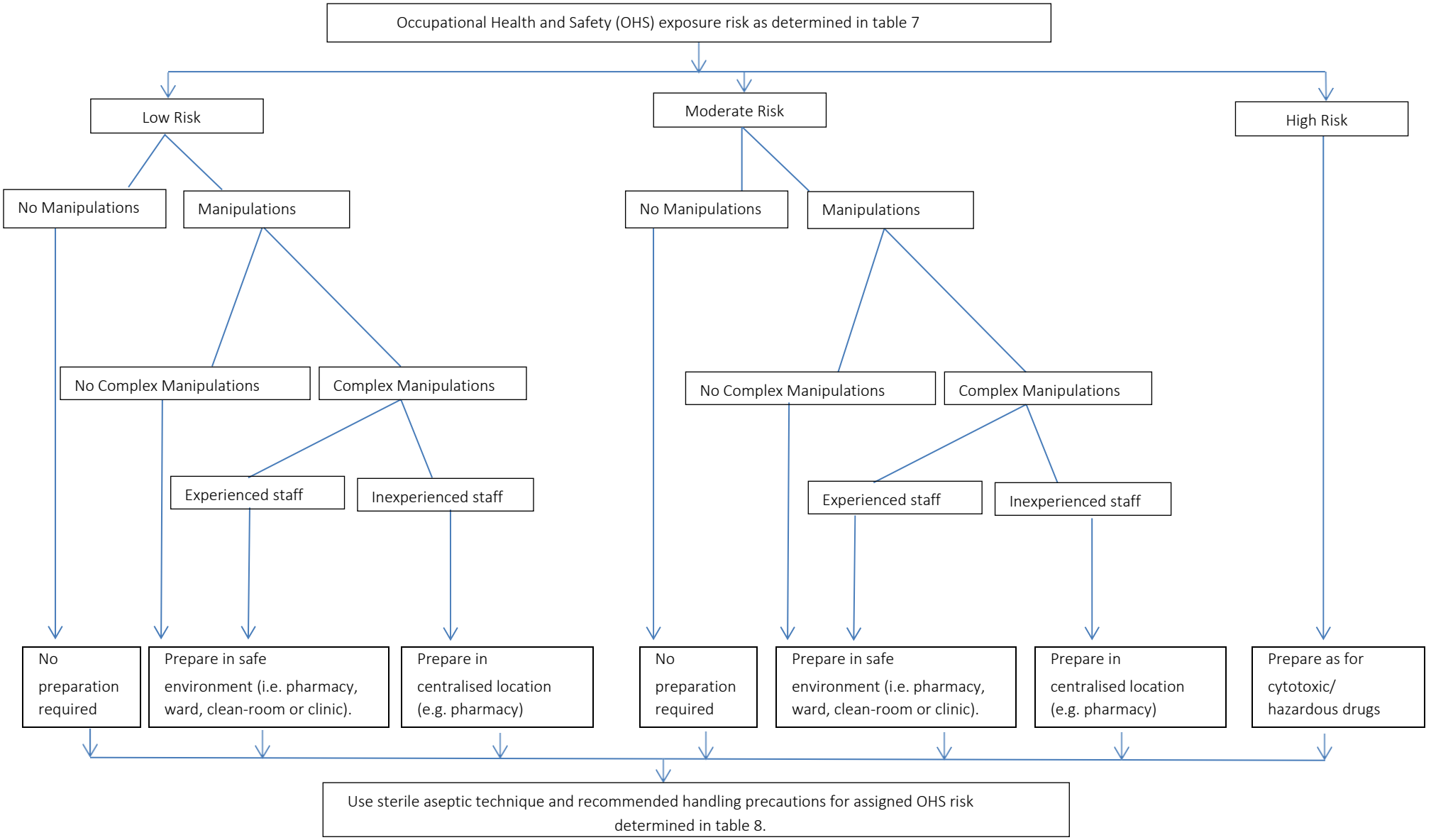
Interpretation of the risk matrix

- Dermal exposure in the workplace setting is likely however with no known mechanism for dermal absorption there is no risk of internalisation (no consequence). No intervention required during the preparation of doses for administration or during administration.
- Oral ingestion is unlikely with the most likely source of exposure being hand to mouth contact. Evidence suggests that internalisation is possible however requires certain idealistic environments (i.e. co-administration with antacid) thus risk of systemic internalisation is low (low consequence). No intervention required during the preparation of doses for administration or during administration.
- Mucosal exposure is possible with internalisation demonstrated in animal models. Exposure is likely to be at very low doses (moderate consequence) and limited to the preparation of doses for administration. No intervention required during administration. Respirator mask and protective eyewear recommended during the preparation of doses for administration.
- Inhalation (powdered or aerosolised particles) is possible, with internalisation demonstrated in animal models. Exposure is likely to be at very low doses (moderate consequence) and limited to the preparation of doses for administration. No intervention required during administration. Respirator mask recommended during the preparation of doses for administration.

2.7.3. Flow Chart (preparation of doses for administration)

Operational and clinical factors influencing the safe handling of MABs may differ according to individual health organisations and should be evaluated by each institution using the flow chart on the next page (figure 1 - *Preparation of doses for administration*). Worked examples are included in section 6 of this document.

Figure 1 – Preparation of doses for administration



– Experienced staff have been given sufficient training (aseptic technique, product knowledge and product specific special instructions (e.g. specific reconstitution techniques, gentle mixing)) required to perform complex manipulations.
– Each institution is unique (in terms of staffing, available skill set and learning opportunities) – therefore each institution will have differing opinions on which is complex

3. Biosimilar Products

A biosimilar (also known as similar biological medicinal product (SBMP)) is not a generic biological medicine. It is defined as being a version of an already registered biological medicine that has:[83]

Demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies (which are then evaluated by the TGA (which has adopted relevant European Union guidelines)).[84]

Although these guidelines have been developed from a review of the literature involving originator biological medicinal products, biosimilar products should be handled in the same manner as the originator product.

4. Non-Cancer MABs

It is important to note that MABs are not only used in the oncology and haematology setting, but are also used to treat a variety of conditions in areas such as Rheumatology, Nephrology, Neurology, Immunology, Gastroenterology, Dermatology and Cardiology.

Although these guidelines have been developed from a review of literature involving oncology and haematology MABs, the principles from an occupational exposure and product protection quality point of view are the same regardless of the products used.

5. MAB Conjugates

Any MAB conjugated to another hazardous substance (e.g. cytotoxic or radiopharmaceutical agent) should be prepared and handled following guidelines and/or standards for the relevant conjugated agent. The Society of Hospital Pharmacists Australia (SHPA) and the International Society of Oncology Pharmacy Practitioners (ISOPP) provide standards for the preparation and handling of cytotoxic agents.[10,61] The Therapeutic Goods Administration (TGA), Pharmaceutical Inspection Convention's Pharmaceutical Inspection Co-Operation Scheme (PIC/S) and Australia New Zealand Society of Nuclear Medicine (ANZSNM) provide standards for the preparation and handling of radiopharmaceutical agents.[85,86]

6. Practical Application of Guideline Recommendations

6.1. Trastuzumab (Herceptin®)

1. Risk Matrix:

i. Likelihood/Consequence of dermal absorption – likely/none

ii. Likelihood/Consequence of oral absorption – unlikely/low

iii. Likelihood/Consequence of inhalation absorption – possible /moderate during preparation of doses for administration and unlikely/moderate during administration.

iv. Likelihood/Consequence of mucosal absorption – possible /moderate during preparation of doses for administration and unlikely/moderate during administration.

Highest Risk Classification: Moderate Risk

Considering occupational health and safety risk only, trastuzumab requires protective mask and eyewear, in addition to standard operating procedures during the preparation of doses for administration. No additional precautions required during administration, use standard operating procedures.

2. Flow Chart

- Moderate Risk → Manipulations Required → Vial Sharing → Prepare in centralised location (e.g. pharmacy) → Use sterile aseptic technique and precautions as recommended for moderate OHS risk (see above)
  or
- Moderate Risk → Manipulations Required → NO Vial Sharing → Complex Manipulations → Experienced Staff → Prepare in safe environment (i.e. pharmacy, ward, clean-room or clinic) → Use sterile aseptic technique and precautions as recommended for moderate OHS risk (see above).
  or
- Moderate Risk → Manipulations Required → NO Vial Sharing → Complex Manipulations → Inexperienced Staff → Prepare in centralised location (e.g. pharmacy) → Use sterile aseptic technique and precautions as recommended for moderate OHS risk (see above)

6.2. Denosumab (Xgeva®)

1. Risk Matrix:

i. Likelihood/Consequence of dermal absorption – likely/none
ii. Likelihood/Consequence of oral absorption – unlikely/low
iii. Likelihood/Consequence of inhalation absorption – unlikely / moderate
iv. Likelihood/Consequence of mucosal absorption – unlikely / moderate

Highest Risk Classification: Moderate Risk
Considering occupational health and safety risk only, denosumab (Xgeva®) requires protective mask and eyewear, in addition to standard operating procedures during the preparation of doses for administration. No additional precautions required, standard operating procedures for administration.

2. Flow Chart

- Moderate Risk → Manipulations Required → No Vial Sharing → No Complex Manipulations → Prepare in safe environment (i.e. pharmacy, ward, clean- room or clinic) → Use sterile aseptic technique and precautions as recommended for moderate OHS risk (see above).

6.3. Denosumab (Prolia®)

1. Risk Matrix:

i. Likelihood/Consequence of dermal absorption – likely/none
ii. Likelihood/Consequence of oral absorption – unlikely/low
iii. Likelihood/Consequence of inhalation absorption – unlikely /moderate
iv. Likelihood/Consequence of mucosal absorption – unlikely / moderate

Highest Risk Classification: Moderate Risk
Considering occupational health and safety risk only, Denosumab (Prolia®) requires protective mask and eyewear, in addition to standard operating procedures during the preparation of doses for administration. No additional precautions required, standard operating procedures for administration.

2. Flow Chart

- Moderate Risk → No Manipulations required (available as prefilled syringe only) → No Preparation required → Use sterile aseptic technique and precautions as recommended for moderate OHS risk (see above).

6.4. Brentuximab Vedotin (Adcetris®)

1. Risk Matrix:

As a cytotoxic conjugate, Brentuximab-Vedotin is automatically assigned into the high risk category. The internalisation potential of the intact conjugated agent is unknown but likely similar to other MABs. However, in the unlikely event the product became un- conjugated / denatured, internalisation and

exposure risk of the small molecule cytotoxic agent is high. Thus the consequence of absorption for all internalisation routes has been classified as high.

i. Likelihood/Consequence of dermal absorption – likely / high
ii. Likelihood/Consequence of oral absorption – unlikely / high
iii. Likelihood/Consequence of inhalation absorption – possible / high
iv. Likelihood/Consequence of mucosal absorption – unlikely / high

Highest Risk Classification: High Risk
Considering occupational health and safety risk only, brentuximab vedotin is to be treated like a cytotoxic or hazardous substance during the preparation of doses for administration and administration.

2. Flow Chart

- High Risk → Prepare as for cytotoxic/ hazardous drugs → Use sterile aseptic technique and precautions as recommended for high OHS risk (see above).

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Appendix 1 - Comparison of drug properties in select commercially available MABs

Drug	Class	Immunogenic	Teratogenic	Mutagenic	Carcinogenic	MW (kDa)	Prep. Steps	Admin. Route	Formulation
Alemtuzumab[29,87]	Fully humanised MAB	ADA: 8.3% HSR: <1% IRR: 10-35%	No data; unlikely to cross placenta due to molecular size; theoretical risk if it did	No data	No data	150	2	IV	Solution
Bevacizumab[30,88,89]	Fully humanised MAB	ADA: 0.63% HSR/IRR: <5%	Yes; animal studies;	No data	No data	149	2	IV	Solution
Brentuximab Vedotin[90,91]	Antibody Drug Conjugate	ADA: 7-30% HSR/IRR: 12%	Yes; animal studies	Yes; animal studies	No data	153	6-8	IV	Powder
Cetuximab[92-94]	Human-murine MAB	ADA: 3.4% HSR/IRR: 14%	Negative in animal studies; expected based on pharmacology	No; negative in vitro and in vivo tests	No data	152	2-3	IV	Solution
Denosumab[95-98]	Fully humanised MAB	ADA: <1% HSR: 0.9 IRR: nil	Conflicting data	No data; not expected based on pharmacology	No data; not expected based on pharmacology	147	0 (Prolia®) 1 (Xgeva®)	SC	Solution
Ipilimumab[99-101]	Fully humanised MAB	ADA: 1.1% HSR: <1% IRR: <1%	Yes; animal studies	Negative *in vitro* and *in vivo* tests	No; animal studies	148	2	IV	Solution
Ofatumumab[31,102]	Fully humanised MAB	ADA: nil HSR: 4% IRR: 44%	No; animal studies	No; animal studies	No; animal studies	149	300mg=6 2g=23	IV	Solution
Panitumumab[50,103,104]	Fully humanised MAB	ADA: 0.4-3.8% HSR: <1% IRR: 3%	No; animal studies	No data	No data	147	2	IV	Solution
Rituximab[51,105-107]	Human-murine MAB	ADA: 12.7% HSR: 1-10% IRR: 15%	No; post-marketing human case reports & animal studies	No data	No data	144	2	IV, SC	Solution
Trastuzumab[107-110]	Human-murine MAB	ADA: 0.1% HSR: 0.6% IRR: 21-35%	Yes; post-marketing human case reports. No; animal studies	Negative in vitro and *in vivo* tests	No data	148	5	IV, SC	Powder

Trastuzumab- Emtansine[111,112]	Antibody Drug Conjugate	ADA: 5.3% HSR: 2.2% IRR: 1.4%	No data; expected based on pharmacology of emtansine and trastuzumab post-marketing experience.	Aneugenic/ Clastogenic in *ir*No data *vivo* testing, Negative in *in vitro* testing	148	5	IV	Powder

ADA – anti-drug-antibody, HSR – hypersensitivity reaction (all grades), IRR – infusion-related reaction (all grades), kDa – Kilo Dalton, MW – Molecular Weight, Prep – preparatio Admin – administration, IV – intravenous, SC – subcutaneous.

Appendix 2 - Steering Committee

- Michael Green, Director Cancer Services, Western Health, Victoria (Project Sponsor)
- Sue Kirsa, Director of Pharmacy, Peter MacCallum Cancer Centre, Victoria (Project Manager)
- Marliese Alexander, Pharmacist, Peter MacCallum Cancer Centre, Victoria (Project Officer) Julie King, Pharmacist, Western Health, Victoria (Project Officer)
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- Ian Roos, Consumer Representative (previous academic and research scientist with an interest in safety issues), Victoria
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- Andrew Cording, Director of Pharmacy, St Vincent's Hospital, Victoria
- Trevor Saunders, National Executive Committee of the Cancer Nurses Society of Australia, Victoria
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