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

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Abstract

These consensus guidelines provide recommendations for the safe handling of monoclonal antibodies. Definitive recommendations are given for the minimum safe handling requirements to protect healthcare personnel. The seven recommendations cover: (i) appropriate determinants for evaluating occupational exposure risk; (ii) occupational risk level compared with other hazardous and non-hazardous drugs; (iii) stratification of risk based on healthcare personnel factors; (iv) waste products; (v) interventions and safeguards; (vi) operational and clinical factors and (vii) handling recommendations. The seventh recommendation includes a risk assessment model and flow chart for institutions to consider and evaluate clinical and operational factors unique to individual healthcare services. These guidelines specifically evaluated monoclonal antibodies used in the Australian cancer clinical practice setting; however, the principles may be applicable to monoclonal antibodies used in non-cancer settings. The guidelines are only applicable to parenterally administered agents.

Introduction

These Australian consensus guidelines were developed to address uncertainty and variation of practice relating to the handling of monoclonal antibodies (MAB) for cancer treatment by healthcare personnel. Recommendations are made for the minimum safe handling requirements to protect all healthcare personnel with additional consideration to clinical and operational factors that may be unique to individual healthcare centres. This publication is an abridged version of the guidelines with supporting studies and complete reference list available within the full guidelines which are freely accessible through the Western and Central Melbourne Integrated Cancer Service website.

These guidelines were developed in accordance with the principles outlined by the National Health and Medical Research Council (NHMRC) and Turner.[1,2] They were informed from a survey of current practice and from a synthesis of available published information. Recommendations were based largely on an absence of data supporting a practice in the face of potential harm to the operator (or healthcare personnel). Recommendations were developed specifically for MAB used in the treatment of cancer.

Funding: The development of these guidelines was funded by Western and Central Melbourne Integrated Cancer Service (WCMICS) as part of a project commissioned to develop safe handling guidelines for novel anti-cancer agents.
Conflict 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 organisations 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.

MAB used in non-malignant diseases and those in early development clinical trials were not formally evaluated. MAB conjugated to cytotoxic, radioactive or other hazardous compounds were excluded and 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 were deemed applicable to bio-similar products.

Process for guideline development

Governance

To develop the guidelines, a steering committee (SC) of relevant medical, pharmacy, nursing and operational experts was formed. The role of the SC was to provide oversight of project activities. From this group, a management committee (MC) was formed to oversee the stages of the project and to provide governance. 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.

Survey of current practice

Cancer pharmacists, medical oncologists, haematologists and oncology nurses identified from peak body oncology associations were invited to participate in an online nationwide survey. Survey respondents from across Australia ($n = 222$) reported their attitudes and institutional practices regarding the preparation and administration of MAB, availability of institutional guidelines and reasons/rationale (if known) for supporting such practices. Results of the clinician's survey 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. Methodological detail and results from the survey are reported elsewhere.[3]

Synthesis of evidence

Project officers undertook a comprehensive search of the literature (May to September 2013), assessed the eligibility of identified studies and critically appraised and summarised included studies for presentation to the WG. For many recommendations, there was a paucity of high-quality supportive evidence with a predominance of preclinical evaluations, animal studies and expert opinion. Despite numerous studies looking at the various toxicities associated with MAB, 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. This again raised questions about how to translate these findings into the MAB handling setting. Methodological detail and results of the literature review are reported elsewhere.[4]

Levels and grades of recommendations

For each recommendation, the WG assigned a level (I–IV) and grade (A–D) of evidence according to levels and grades of evidence as stipulated by the NHMRC.[5] Where evidence was insufficient to meet even the lowest level of evidence (i.e. preclinical studies) or where no evidence was identified, consensus-based recommendations were given and annotated as good practice points.

Consensus and endorsement

In framing the guideline recommendations, the WG carefully considered the need to balance occupational health with clinical and operational factors associated with the preparation of MAB. Draft recommendations were presented at two consensus meetings, which 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. At each meeting, consensus opinion was invited for all recommendations presented by the WG. Consensus was defined as unanimous, majority or no-consensus. Consensus was obtained across both meetings on all draft recommendations. These were then used as the basis for the development of final recommendations from the WG, which obtained further consensus through endorsement from various stakeholder groups.

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, Cancer Nurses Society of Australia, Clinical Oncology Society of Australia (COSA), COSA Cancer Pharmacists Group, MOGA, Pharmacy Guild of Australia and the Society of Hospital Pharmacists of Australia.

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 have reviewed and provided support for the guidelines, including distribution and reference within the organisation. The Australian Nursing and Midwifery Federation 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.

Guideline recommendations

The guidelines include seven major recommendations (Table 1) with the final recommendation detailing safe handling recommendations. Handling recommendations were based on evidence and rationale from the previous recommendations and include a risk matrix for assessment of occupational exposure risk and determination of minimum safe handling requirements (Tables 2,3) and a flow chart guiding safe handling recommendations for various operational and clinical scenarios (Fig. 1). Any agent lacking sufficient information to assign a risk category (such as clinical trial agents) was stipulated to be treated as high risk until additional information becomes available.

Recommendation I: occupational exposure risk evaluation

Occupational health and safety risks to healthcare personnel who handle MAB 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. While evidence exists for the internalisation of therapeutically administered MAB through inhalation, mucosal and oral routes, the ability to achieve systemic bioavailability in the occupational exposure setting was considered to be limited (Table 4). The applied criteria for toxicity was adapted from hazardous substance criteria defined by the Australian National Occupational Health and Safety Commission (now Safe Work Australia) and the United States National Institute for Occupational Safety and Health for hazardous chemicals,[6,7] with the addition of immunogenicity (specific concern of MAB and other immunomodulatory agents) and cytotoxicity (applicable as MAB are commonly treated as cytotoxic agents) (Table 5).

Table 1 Summary of recommendations

Recommendation	Level – grade†
I. That the occupational health and safety risk to healthcare personnel handling MAB is dependent on the following risk factors:	
i. Internal exposure risk	
• through dermal absorption	GPP
• through inhalation absorption	GPP
• through mucosal absorption	GPP
• through oral absorption	IV-D
ii. Toxicity	
• cytotoxicity	GPP
• carcinogenicity	II-C
• genotoxicity or mutagenicity	GPP
• teratogenicity or other developmental toxicity	IV-D
• organ toxicity at low doses	GPP
• immunogenicity	III-D
II. From an occupational health and safety perspective, it would be prudent for MAB 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
III. Safe handling procedures should be stratified according to:	
i. Healthcare staff role (preparation, administration, transportation/disposal)	III-D
ii. Health considerations (e.g. pregnancy)	GPP
IV. Procedures for the handling of waste generated during the preparation or clinical use of MAB are as follows:	
i. Waste products generated during the preparation of MAB should be disposed as per standard operating procedures for parenterally administered agents, that is, not classified as cytotoxic waste	GPP
ii. Waste products and/or bodily fluids of patients who have been administered MAB should be disposed as per standard operating procedures for parenterally administered agents, that is, not classified as cytotoxic waste	GPP
V. The range of available interventions/safeguards to minimise occupational exposure are:	
i. Personal protective equipment (PPE)	
• Gloves	III-D
• Gown	GPP
• Respirator mask	GPP
• Protective eyewear	GPP
ii. Discipline based aseptic technique	III-D
iii. Isolator cabinet	GPP
iv. Cytotoxic drug safety cabinet)	GPP
v. Closed system drug transfer devices	III-D
And use of these should be risk stratified according to risk of internal exposure and toxicity	
VI. That the following factors (not related to occupational exposure risk) should be considered when determining preparation and handling recommendations	
i. Vial sharing	GPP
ii. Complexity of preparation	GPP
iii. Medication error	GPP
VII. MAB handling recommendations consider occupational health and safety risks as well as operational and clinical factors	GPP

†Level and grades of evidence assigned according to National Health and Medical Research Council criterion. GPP, good practice points; MAB, monoclonal antibodies.

Table 2 Risk matrix (occupational health and safety risk assessment)

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.

Recommendation II: hazard classification

From an occupational health and safety perspective, it would be prudent for MAB to require greater handling precautions than other non-hazardous injectable medications; however, they do not warrant full cytotoxic precautions. The WG considered that although toxicity profiles may vary, all currently available MAB have a similar low risk of internalisation at occupational exposure levels. Safe handling recommendations within this guideline were therefore deemed applicable to all MAB (class effect). Future development of MAB 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 reassessed according to risk factors identified in recommendation I of these guidelines. Refer to Table 6 for a comparison of drug properties in selected Australian commercially available MAB.

Table 3 Recommended safe handling precautions (based on risk matrix assessment)

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[39]).

Recommendation III: occupational exposure risk stratification

There was no evidence regarding teratogenicity resulting from occupational exposure to MAB. In the event of occupational exposure and subsequent internalisation, it was considered possible that a pregnant woman may be at risk of teratogenic effects that have been observed at therapeutic doses. Some manufacturers recommend pregnant personnel avoid handling, while others contain no information. Given that MAB exert their effect through 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. Without evidence to demonstrate safety, the WG recommend that healthcare personnel with relevant health considerations (pregnancy, immunosuppression or other) should avoid the preparation of doses for administration, where exposure risk is the greatest.

Recommendation IV: waste products

MAB do not have direct cytotoxic activity, and no known or potential mechanism of internalisation through dermal contact, the most likely form of contact when cleaning or disposing of contaminated waste products. Exposure to waste products does not present an occupational health and safety risk to healthcare personnel beyond that of other parenterally administered agents. The likelihood that active and/or toxic metabolites are present in patient waste is highly improbable. The proteinaceous nature of MAB renders them liable to digestion and breakdown prior to elimination. Furthermore, the targeted action and durable effects of MAB correspond to retention in the body for weeks after administration. Excluding MAB conjugated to cytotoxic, radioactive or other hazardous substances, the risk of bioconversion to toxic metabolites was perceived to be low. Exposure to patient waste products and/or bodily fluids does not present an occupational health and safety risk to healthcare personnel.

Recommendation V: interventions and safeguards

Currently available and commonly used personal protective equipment, pharmaceutical manufacturing equipment and operator techniques were evaluated for applicability to the safe handling of selected anticancer MAB (Table 6). For protection of healthcare personnel, only respirator masks and protective eyewear were considered necessary to protect against inhalation and

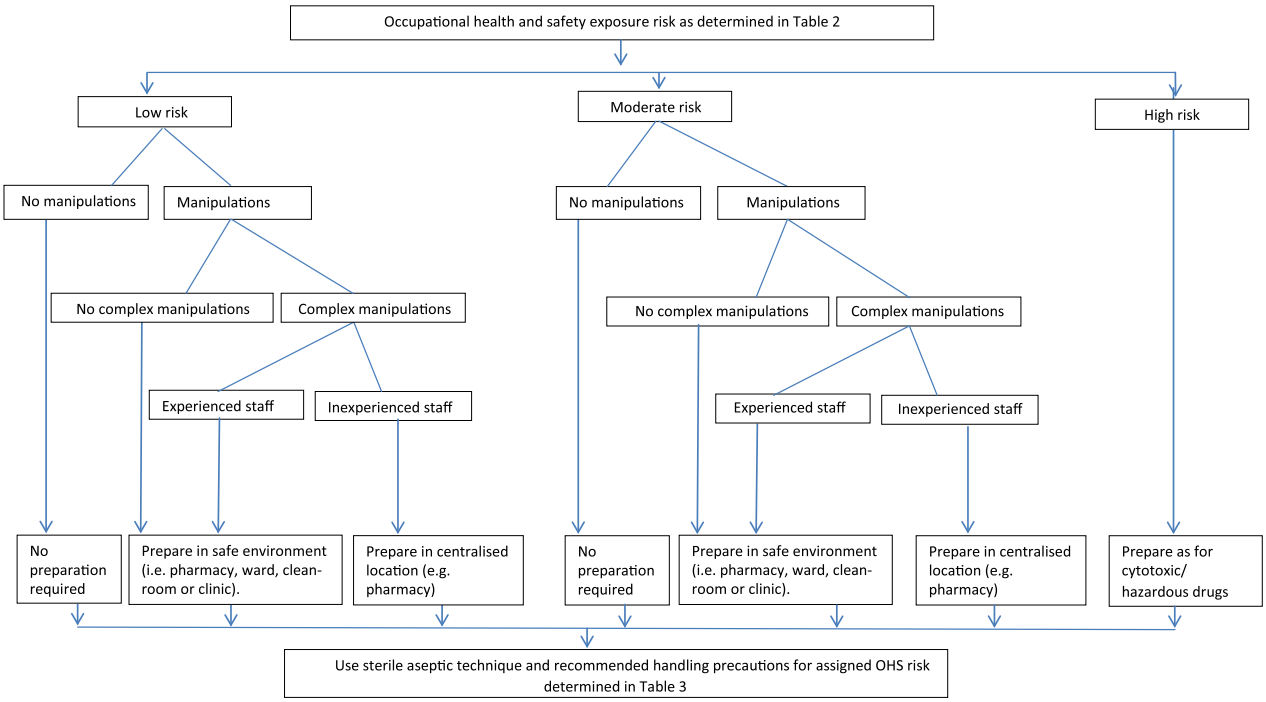

Figure 1 Preparation of doses for administration.

mucosal absorption. For protection of the product, discipline-based aseptic technique, including wearing gloves, should be implemented for the preparation of doses for administration as per any other injectable pharmaceutical. Appropriate aseptic technique is described by the Australian Commission on Safety and Quality in Healthcare.[39] Closed system drug transfer devices, pharmaceutical manufacturing cabinets (isolator cabinets or cytotoxic drug safety cabinets) and sterile manufacturing units were not considered necessary to protect against occupational exposure.

Recommendation VI: operational and clinical factors

Vial sharing

Good practice recommendations and pharmaceutical product information sheets state that opened or used vials should not be shared. Risks pertain both to the possibility of cross-contamination between shared vials prepared for immediate use and to the storage of vials (stability, sterility and expiry) for use at a later time or date. Anecdotal evidence from individual institution procedures suggest that only when compounding occurs in a pharmacy under aseptic conditions is it appropriate to vial share. The Australian funding model through the Pharmaceutical Benefits Scheme (PBS) reimburses costs of chemotherapy drugs based on using the most efficient combination of available vial strengths to achieve a given dose.[40] In some circumstances, this may result in residual volume and may influence a preference towards vial sharing. Vial sharing, while not recommended by manufacturers and not endorsed by major health and safety bodies, does occur in routine clinical practice. While increasing risks associated with microbial contamination, the practice of vial sharing in the preparation of MAB is no different to vial sharing for other parenteral medicines, and institutions should follow local existing policy relating to this practice.

Complexity of preparation

As the number of preparation steps increases, 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.[41,42] Most MAB require between two to eight manufacturing steps, with high dose ofatumumab requiring up to 23 manipulations. Denosumab (non-oncology indication) is currently the only MAB available in Australia as a ready-to-use formulation (pre-filled

Table 4 Internal exposure risk†

Exposure	Recommendation(s)
Dermal	Based on physiochemical (molecular size) and pharmacokinetic (permeability profile) properties, dermal absorption of MAB was not considered to be a viable mechanism of internalisation. The risk of contact allergy is associated with excipients (such as tensides) rather than active agents (MAB) and was considered to be no different to other pharmaceutical products containing commonly used excipients.
Inhalation	Based on demonstrated internalisation in therapeutic animal models, inhalation was considered to be a viable route of internalisation with unquantified and indeterminate effects at long-term low-dose exposure levels. Exposure risk was considered to be the greatest during the preparation of doses for administration where staff may be exposed to powdered or aerosolised liquid particles.
Mucosal	Based on demonstrated internalisation in therapeutic animal models (intranasal, vaginal and ocular drug delivery), mucosal absorption was considered to be a viable route of internalisation with unquantified and indeterminate effects at long-term low-dose exposure levels. Exposure risk was considered to be the greatest during the preparation of doses for administration and although possible, unlikely to occur through contamination within other workspaces in the occupational setting.
Oral	Based on demonstrated stability in preclinical studies and internalisation in therapeutic animal and human models, oral ingestion was considered a viable route of internalisation with unquantified and indeterminate effects at long-term low-dose exposure levels. Although viable, internalisation required idealistic conditions and occupational exposure at levels required for systemic bioavailability was considered to be highly unlikely.

†Refer to full guidelines hosted on the Western and Central Melbourne Integrated Cancer Service website for study details and citations. MAB, monoclonal antibodies.

Table 5 Toxicity†

Criteria	Recommendation(s)
Cytotoxicity	Immune-mediated cytotoxicity, important for the therapeutic efficacy of some MAB, is explicitly different to the direct cytotoxic action of traditional anticancer agents. It was therefore considered that MAB admixtures should not be labelled as 'cytotoxic' or 'treat as cytotoxic', unless there is evidence to the contrary.
Carcinogenicity	Based on data from clinical drug trials and post-marketing research, some MAB are potentially carcinogenic at therapeutic doses. Effects at long-term low-dose exposure levels are unquantified and indeterminate.
Genotoxicity/ mutagenicity	MAB are not required to be evaluated for genotoxicity. Based on safety and immunotoxicity assessment, immunomodulatory MAB do not interact directly with DNA and hence were considered to be neither genotoxic nor mutagenic.
Teratogenicity/ developmental toxicity	Based on animal studies and post-marketing research, some MAB are teratogenic at therapeutic doses with unquantified and indeterminate effects at long-term low-dose exposure levels.
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. Extrapolation of toxicity profiles from therapeutic doses may be misleading considering evidence relating to (lack of) potential occupational exposure internalisation routes. However, owing to the long elimination half-life of MAB, this must be balanced with the risk of continuous exposure and drug accumulation.
Immunogenicity	Based on clinical studies and post-marketing data, immunogenicity may occur at therapeutic exposures to some MAB, with unquantified and indeterminate effects at long-term low-dose exposure levels. Immunogenic reactions are more likely with murine then chimeric then fully humanised MAB. The consequence of immunogenic reaction relating to toxicity and/or efficacy is unclear.

†Refer to full guidelines hosted on the Western and Central Melbourne Integrated Cancer Service website for study details and citations. MAB, monoclonal antibodies.

syringe); however, it is likely that ready-to-use formulations for subcutaneous administration of other agents will soon enter the market. 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, while in other institutions, this may be best achieved and monitored in a controlled manufacturing environment, such as a pharmacy cleanroom.

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. Unlike traditional chemotherapeutic agents, MAB have a large therapeutic window and as such need not be considered within high-risk medication lists (e.g. A-PINCH acronym used by the Clinical Excellence Commission identifies classes of medicines deemed high risk;

Table 6 Comparison of drug properties in select commercially available monoclonal antibodies (MAB)

Drug	Class	Immunogenic	Teratogenic	Mutagenic	Carcinogenic	MW (kDa)	Prep. Steps	Admin. Route	Formulation
Alemtuzumab[8,9]	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[10–12]	Fully humanised MAB	ADA: 0.63% HSR/IRR: <5%	Yes; animal studies;	No data	No data	149	2	IV	Solution
Brentuximab Vedotin[13,14]	Antibody drug conjugate	ADA: 7–30% HSR/IRR: 12%	Yes; animal studies	Yes; animal studies	No data	153	6–8	IV	Powder
Cetuximab[15–17]	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[18–21]	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	0–1	SC	Solution
Ipilimumab[22–24]	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[25,26]	Fully humanised MAB	ADA: nil HSR: 4% IRR: 44%	No; animal studies	No; animal studies	No; animal studies	149	300 mg = 6 2 g = 23	IV	Solution
Panitumumab[27–29]	Fully humanised MAB	ADA: 0.4–3.8% HSR: <1% IRR: 3%	No; animal studies	No data	No data	147	2	IV	Solution
Rituximab[30–33]	Human-murine MAB	ADA: 12.7% HSR: 1–10% IRR: 15%	No; post-marketing human case reports and animal studies	No data	No data	144	2	IV, SC	Solution
Trastuzumab[33–36]	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[37,38]	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 *in vivo* testing, Negative in *in vitro* testing	No data	148	5	IV	Powder

ADA, anti-drug-antibody; Admin, administration; HSR, hypersensitivity reaction (all grades); IRR, infusion-related reaction (all grades); IV, intravenous; kDa, kilodalton; MAB, monoclonal antibodies; MW, molecular weight; Prep, preparation; SC, subcutaneous.

anti-infectives, potassium and other electrolytes, insulin, narcotics and other sedatives, chemotherapeutic agents and heparins and other anticoagulants).[43] The WG considered that medication 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, while in other institutions, this may be best achieved and monitored in a controlled manufacturing environment, such as a pharmacy cleanroom.

Recommendation VII: handling recommendations

Safe handling recommendations were based on risk of internalisation and toxicity (established using risk matrix; Tables 2,3) and with due regard to operational and clinical factors (established using flow chart; Fig. 1). Overall risk of exposure was assessed based on likelihood of exposure and risk of internalisation. Within the risk matrix, likelihood of exposure refers to the likelihood that healthcare personnel will be exposed to MAB. 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. Operational and clinical factors influencing the safe handling of MAB may differ according to individual health organisations as detailed in recommendation VI.

To determine the most appropriate handling precautions for an individual, MAB first assign an occupational health and safety risk category (Table 2). Second, determine appropriate handling requirements (Table 3). Third, take the assigned risk category and utilise the flow chart (Fig. 1) to determine the recommended location for the preparation of doses for administration, based on various clinical and operational scenarios. Recommendations apply to the handling of MAB during the preparation of doses for administration, during the 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 and training and careful risk management steps should be undertaken.

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