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A survey of manufacturing and handling practices for monoclonal antibodies by pharmacy, nursing and medical personnel

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Abstract

Introduction: There is a paucity of data available to assess the occupational health and safety risk associated with exposure to monoclonal antibodies. Industry standards and published guidelines are conflicting or outdated. Guidelines offer contrary recommendations based on an array of methodological approaches. This survey aimed to describe current practices, beliefs and attitudes relating to the handling of monoclonal antibodies by Australian medical, nursing and pharmacy clinicians.

Methods: An electronic survey was distributed between June and September 2013. Respondents were surveyed on three focus areas: institutional guideline availability and content, current practices and attitudes. Demographic data relating to respondent and primary place of practice were also collected.

Results: A total of 222 clinicians completed the survey, with representation from all targeted professional groups and from a variety of geographic locations. 92% of respondents reported that their institution prepared or administered monoclonal antibodies, with 87% specifically handling anti-cancer monoclonal antibodies. Monoclonal antibodies were mostly prepared onsite (84–90%) and mostly within pharmacy clean-rooms (75%) and using cytotoxic cabinets (61%). 43% of respondents reported access to institutional monoclonal antibody handling guidelines with risk reduction strategies including training and education (71%), spill and waste management (71%), procedures for transportation (57%) and restricted handling (50%). Nurses had a stronger preference towards pharmacy manufacturing than both doctors and pharmacists for a range of clinical scenarios. 95% of all respondents identified that professional or regulatory body guidelines are an important resource when considering handling practices.

Conclusion: Monoclonal antibodies are most commonly handled according to cytotoxic drug standards and often in the absence of formal guidelines.

Keywords

Cancer, occupational exposure, guidelines, survey, monoclonal antibodies

Introduction

Monoclonal antibodies (MABs) are being rapidly introduced into medical oncology and haematology clinical practice with widespread application in the treatment and supportive care of cancer patients. There is a paucity of data available to assess the occupational health and safety risk associated with exposure to these molecules. Dissimilarities in both chemical and physical properties of MABs, as compared with traditional cytotoxic anticancer agents, limit the ability to extrapolate safety data regarding occupational exposure risk. This is particularly relevant when assessing the ability of healthcare workers to internalise (the rate-limiting step in systemic bioavailability and toxicity) these agents in the context of occupational exposure. MABs either do not fulfil conventional hazardous substance criteria or lack sufficient agent-specific information to assign an appropriate hazard classification. Hazardous substance lists and criteria from the National Occupational Health

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and Safety Commission (NOHSC) of Australia (now Safe Work Australia) and the National Institute for Occupational Safety and Health (NIOSH) of America do not include any major anticancer MABs.[1,2] NOHSC criteria were derived from European Community's legislation for classifying dangerous substances,[3–5] while the NIOSH criteria were adapted from criteria developed by the American Society of Hospital Pharmacists.[6] Withstanding minor differences in terminology and phrasing, both criteria are fundamentally equivocal and consider toxicity (acute and chronic), carcinogenicity, mutagenicity/genotoxicity, and teratogenicity (toxicity to reproduction, fertility and/or development).[7,8]

Australian industry standards for the safe handling and exposure risk associated with MABs are conflicting and outdated. Occupational health and safety and dangerous substances legislative documents do not include reference to MABs or other new anticancer agents.[7,9–11] Similarly, occupational health and safety authorities, under the umbrella of Safe Work Australia, do not provide recommendations relating to the handling of these agents.[12] The most recent publication of relevance by Work Safe Victoria 'Handling cytotoxics in the workplace 2003' does not mention MABs.[12] A more recent publication by the South Australian government 'Safe handling of hazardous drugs and related wastes 2012' discusses MABs; however, it does not provide formal handling recommendations.[13] The Society of Hospital Pharmacists of Australia (SHPA) recommends that until definitive research proves otherwise, MABs should be handled in dedicated negative pressure (containment) clean areas to prevent exposure.[14] Material safety data sheets from pharmaceutical companies provide varying levels of recommendations: no special control measures (ofatumumab),[15] restriction of handling to specific areas and by restricted personnel (cetuximab),[16] use of personal protective equipment (PPE) with respiratory protection (ipilimumab)[14] or without respiratory protection (bevacizumab)[17] and handling in enclosed processes or within a chemical hood (panitumumab).[18]

In recent years, several guidelines (published and unpublished) for the safe handling of MABs have been developed,[19–25] unfortunately confounding rather than clarifying the issue of safe handling and occupational exposure risks. Guidelines have employed differing methodological approaches considering a range of drug and occupational factors. Handling recommendations have been formulated based on unknown occupational safety risk (i.e. maximum precaution until further evidence);[14] MAB origin;[23] MAB origin, toxicity and complexity of dosing and manufacturing;[25] complexity of manufacturing, clinical risk (patient safety) and toxicity;[22] clinical risk and toxicity[24] and toxicity and risk of internalisation.[20,21] Recommendations using these methodologies range from minimal PPE (gloves) to full cytotoxic precautions.

Consequential to this wide array of recommendations and omissions within key regulatory, industry and professional body documents, correct handling procedures and safety precautions are uncertain. MABs are being handled both according to cytotoxic standards (i.e. pharmacy clean room) and with limited safety precautions (i.e. at the bedside). The default of handling MABs as cytotoxic agents results in the use of handling standards that may be overcautious. Implications include decreased efficiency, increased costs (despite compounding rebates) 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, hospital-only treatment). Conversely, an unconsidered approach may place staff at risk or result in adverse clinical effects and significant financial cost as a result of erroneous manufacturing technique and potential compromise of product integrity. A French survey of handling practices reported that 92% of MABs were prepared as for cytotoxic agents (hospital pharmacy-based centralised areas, isolators, safety cabinets and exhaust fans).[26] Interestingly, the same survey found that half of the healthcare personnel regarded their own occupational risk as low.

This study describes current practices, beliefs and attitudes relating to the handling of MABs from the perspective of medical, nursing and pharmacy clinicians in the Australian healthcare setting. The results of this survey were used to guide the development of Australian consensus guidelines for the safe handling and administration of MABs for cancer treatment by healthcare personnel.

Methods

Population

Medical, pharmacy and nursing personnel working in Australian healthcare and pharmaceutical manufacturing industries holding current membership with targeted professional organisations: Cancer Nurses Society of Australia (CNSA), Clinical Oncology Society of Australia (COSA), Haematology Society of Australia and New Zealand (HSANZ), Medical Oncology Group of Australia (MOGA) and SHPA.

Study design

A multi-disciplinary survey of current practice and opinion relating to the handling of MABs was

developed using Survey Monkey® software. Peter MacCallum Cancer Centre ethics approval was obtained (approval number: 13/49 L). Respondents were surveyed on three focus areas: demographics, institutional guidelines and current practices and attitudes. Demographics included profession (nurse, pharmacist or doctor), specialisation (medical oncology or haematology) and description of primary place of practice (location, number of beds). Availability of institutional guidelines included dichotomous (yes/no) and qualitative assessment. Opinions and current practices were established by asking respondents about the handling of a range of MABs (bevacizumab, brentuximab vedotin, cetuximab, denosumab, rituximab and trastuzumab) chosen to represent the range of available dose forms and manufacturing and administration techniques of commonly used MABs. The survey was piloted locally, with assessments providing an opportunity to improve clarity and focus of questions prior to wider distribution.

Data collection and analysis

Distribution of the survey was staggered between June and September 2013 based on timing of approval and distribution of the survey by the relevant professional organisation. In all cases, the survey was distributed electronically with a reminder email after 2 weeks and response cut-off after 8 weeks. The total number of individuals surveyed (and hence response rate) is not reported due to an assumed substantial proportion of co- or multi-membership holders, who would have received the survey multiple times. All responses were anonymous and consent to participate was obtained as the first survey question with automatic termination if consent was not provided. All responses were included in analyses with data aggregated and presented using simple descriptive statistics. Two-sample tests of proportions were used to report on the significance of differences in responses according to respondent's profession (nursing, pharmacy and medical).

Results

Consent and subsequent survey completion was achieved by 222/223 (99.6%) of clinicians who accessed the survey. Respondents were from across Australia and New Zealand and represented a variety of health services including metropolitan, regional, public and private centres. Pharmacy personnel constituted the majority of respondents ($n = 113$, 51%), followed by nurses ($n = 50$, 22%) and doctors ($n = 46$, 21%); 13 (5%) respondents did not provide an answer to this question. Detailed respondent professional information is shown in Table 1.

Table 1. Respondent demographics.

	n (%)
Primary place of practice	
Location	
Victoria	117 (52.7)
New South Wales	31 (14)
Queensland	24 (10.8)
Western Australia	12 (5.4)
Other	22 (9.9)
Not specified	16 (7.2)
Rurality	
Metropolitan/major city	155 (69.8)
Regional/rural	51 (23)
Not specified	16 (7.2)
Institution type	
Hospital or clinic	196 (88.2)
External pharmacy compounder	10 (4.5)
Not specified	16 (7.2)
Public or private	
Public only	167 (75.2)
Private only	32 (14.4)
Public/private even split	7 (3.2)
Not specified	16 (7.2)
Institution size	
No inpatient beds	6 (2.7)
≤150 beds	55 (24.8)
151–300 beds	32 (14.4)
301–500 beds	52 (23.4)
≥500 beds	35 (15.8)
Not specified	42 (18.9)
Profession and specialisation	
Doctor	46 (21)
Medical oncology	25 (54.3)
Haematology	14 (30.4)
Both	7 (15.2)
Head of department or tumour stream	14 (30.4)
Consultant	29 (63.0)
Fellow or registrar	3 (6.5)
Pharmacy personnel	113 (51)
Pharmacist	109 (96.5)
Pharmacy technician	4 (3.5)
Oncology	72 (63.7)
Non-oncology	37 (33.9)
Clinical	59 (54.1)
Manufacturing	30 (27.5)
Management	24 (22.0)
Nurse	50 (22)
Oncology	48 (96.0)

(continued)

Table 1. Continued.

	n (%)
Non-oncology	2 (4.0)
Clinical	38 (76.0)
Management	4 (8.0)
Other (education, trials, research)	5 (10.0)
Profession not specified	14 (6)

Table 2. Strategies currently employed to reduce employee exposure risk to MABs, *n* (%).

Strategy	*n* (%)
Staff training and education on the potential hazards	136 (70.8)
Procedures for dealing with spillages and disposal	136 (70.8)
Procedures for transportation	109 (56.8)
Restrictions for employees who are pregnant, planning a pregnancy or breastfeeding	95 (49.5) 95
Storage in a designated, well sign posted section of the work area	72 (37.5)
Stored separately from other cytotoxic agents	28 (14.6)
No strategies; no perceived risk to employees handling these agents	7 (3.7)
No strategies; there are perceived risks, but no action taken	15 (7.8)
Not Sure	27 (14.1)
Other Other (please specify)	22 (11.5) 22
Total respondents	192 (100.0)

MABs: monoclonal antibodies.

The majority of respondents (205/222, 92%) reported that their institution handled (prepared or administered) MABs, with most (194/222, 87%) handling anti-cancer MABs. A total of 95 (43%) respondents reported access to institutional MAB handling guidelines. Among those with guidelines, 74 (78%) reported 'good' compliance to recommendations. Strategies implemented to reduce the risk of occupational exposure are shown in Table 2. Among clinicians providing an evaluation of institutional guidelines, the most common strategies employed to reduce risk were training and education (71%), spill and waste management (71%), procedures for transportation (57%) and restricted handling (50%).

For all MABs included in the survey, the majority of clinicians (84–90%) prepared (manufactured) agents onsite. For the range of MABs included in the survey, the majority of respondents (overall median: 75%, overall range: 37–88%) prepared MABs in pharmacy clean-rooms, Figure 1. A total of 61% utilised cytotoxic down flow cabinets, 15% closed system drug transfer devices, 6.8% laminar cross flow cabinets, 4.8% biohazard cabinets and 2.9% clean area within pharmacy. Variation in reported handling practices was most notable for denosumab and trastuzumab. A total of 51% of clinician's reported preparation of denosumab on the ward compared with 38% in a pharmacy cleanroom, with an opposing trend for trastuzumab: 11% prepared on the ward compared with 74% in a pharmacy clean room. Reported use of PPE varied among agents and among respondents, Figure 2.

Attitudes regarding the occupational exposure risk and hence required handling procedures for MABs are reported for 172 clinicians, with notable differences by profession. 80% of nurses compared with 50% of doctors ($p = 0.011$) and 44% ($p < 0.001$) of pharmacists strongly agreed that all MAB admixtures should be prepared in pharmacy clean rooms. 70% of nurses compared with 51% of doctors ($p = 0.014$) and 45% of pharmacists ($p = 0.015$) strongly agreed that drugs to be given to immunocompromised patients should be prepared in pharmacy clean rooms. 80% of nurses compared with 49% of doctors ($p = 0.008$) and 65% of pharmacists ($p = 0.129$) strongly agreed that drugs with complex manufacturing requirements should be prepared in pharmacy clean rooms. Nurses had a stronger preference towards pharmacy manufacturing than both doctors and pharmacists for a range of additional clinical scenarios, Figure 3.

Respondents were surveyed on the importance of independently produced guidelines (external regulatory or professional body guidelines) for the handling of MABs. Of those who responded, 21/28 (75%) nurses, 62/95 (65%) pharmacists and 15/35 (43%) doctors strongly agreed that they are important in considering handling practices. Factors influencing MAB handling practices, presented by respondent profession, are shown in Figure 4. All groups (170/172, 99% of respondents) agreed that evidence of mutagenicity, teratogenicity or carcinogenesis in patients of healthcare workers is an important factor when considering the location for the preparation of MABs. The molecular size and weight of MABs (magnitudes higher than traditional cytotoxic chemotherapy), was considered important (agree or strongly agree) by 31%, 45% and 54% of medical, pharmacy and nursing personnel respectively. Other factors reported to influence preparation included pharmaceutical company and professional or regulatory body guidance, the type of preparation (e.g. formulation, number of vials required and complexity of manipulations) as well as the ability to provide timely access to treatment.

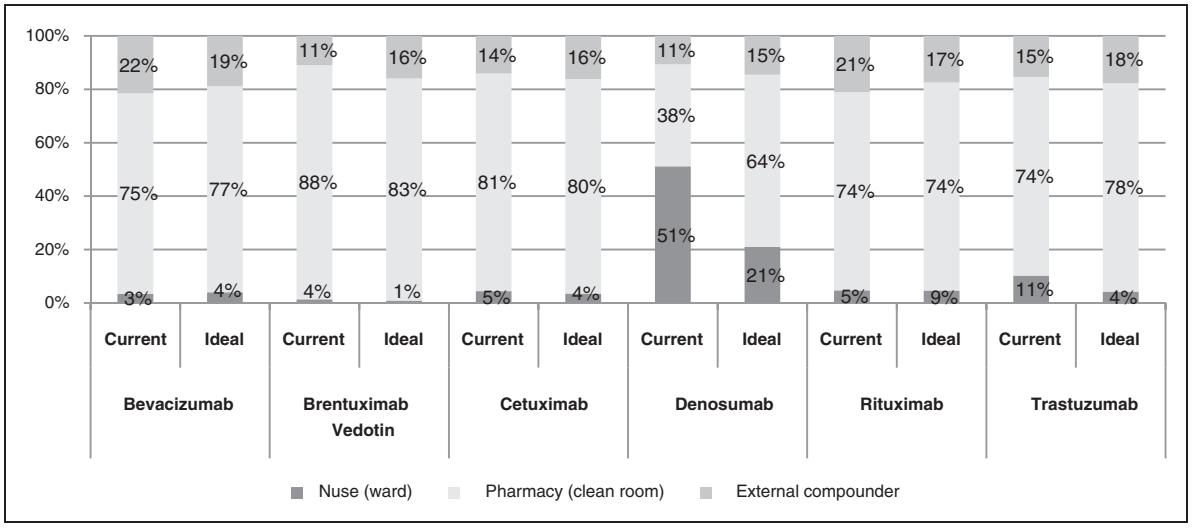

Figure 1. Current versus ideal MAB manufacturing practices.
MAB: monoclonal antibody.

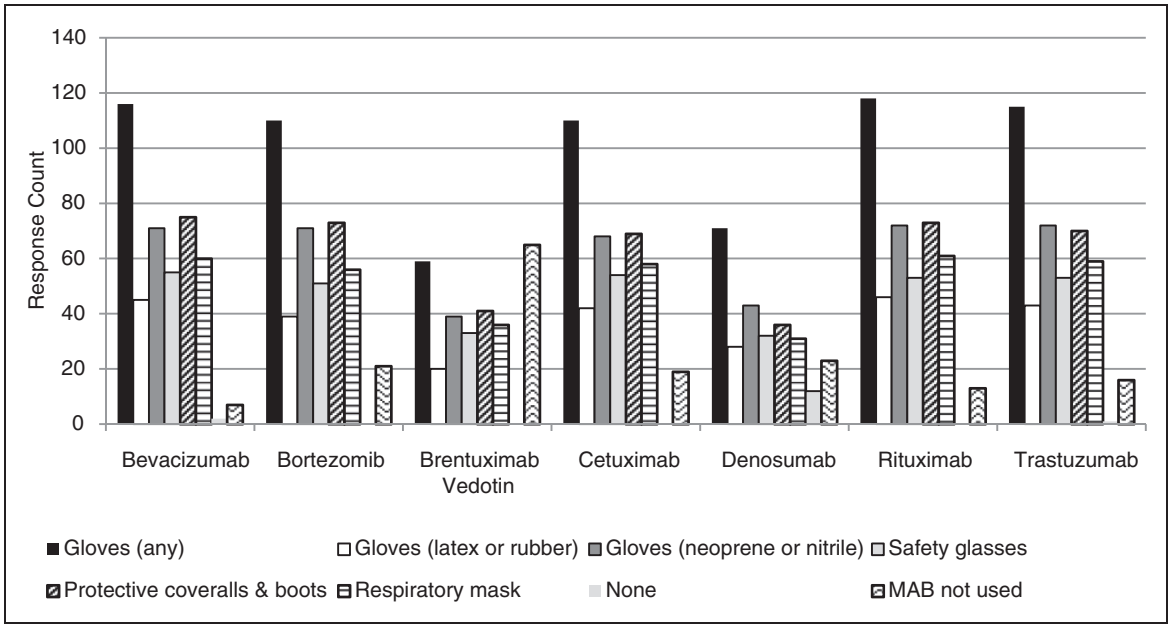

Figure 2. Use of PPE during MAB preparation.
MAB: monoclonal antibody; PPE: personal protective equipment.

Discussion

This is the first published study reporting handling practices of MABs in healthcare services across Australia. More than 90% of respondents reported preparation, handling or administration of MABs at their healthcare institution; yet less than 50% reported access to MAB handling guidelines. Furthermore, respondents from all professional groups (>95% of all respondents) identified that professional or regulatory body information (i.e. independently produced guidelines) is an important resource when considering handling practices. The results are felt to be generalisable across Australia with responses from a variety (geographic location, size and services offered) of healthcare institutions. Acknowledgment should however be given to the large proportion of Victorian respondents, a potential bias and likely influence from

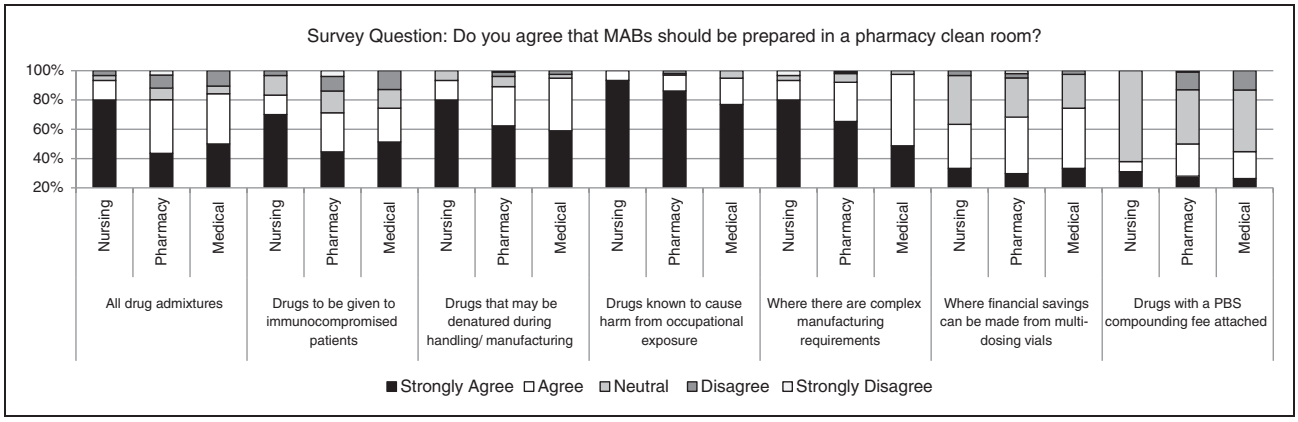

Figure 3. Attitudes regarding the handling of MABs by profession.
MABs: monoclonal antibodies.

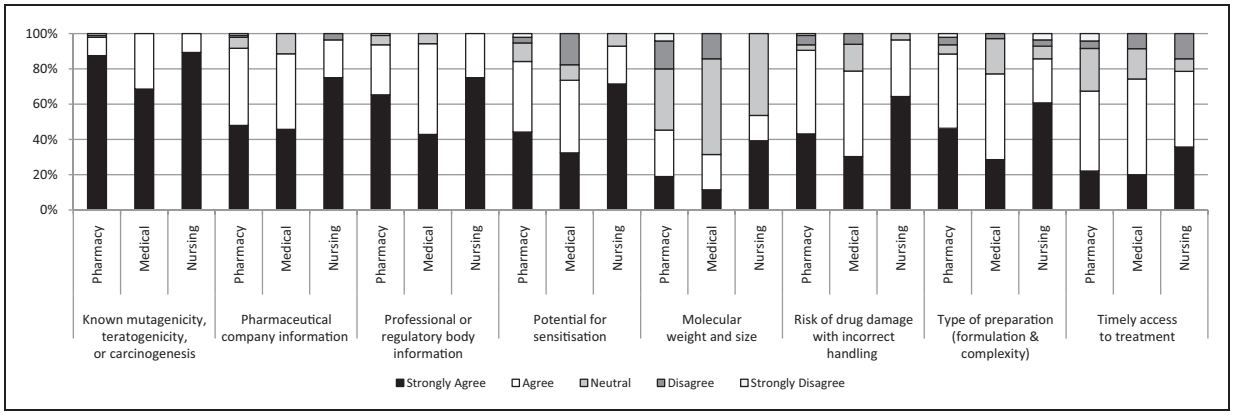

Figure 4. Factors influencing decisions regarding handling precautions and manufacturing location by profession.

key project personnel who practice in Victorian hospitals. Reassuringly, project personnel were dispersed across five Victorian healthcare services ranging from specialist oncology centres to large general hospitals.

Survey results demonstrate that the majority of MABs are prepared using full cytotoxic precautions (cytotoxic cabinet in pharmacy, full PPE). This common practice remains despite neither NOHSC (Safe Work Australia) nor NIOSH listing these agents as hazardous substances. Perhaps demonstrating a belief that this is an omission of classification rather than classification that these agents are truly non-hazardous. This is supported by findings that respondents equally prefer (ideal manufacturing practices) the pharmacy manufacturing of brentuximab vedotin (MAB conjugated to a cytotoxic agent) and cetuximab (unconjugated MAB), 83% and 80% of respondents, respectively.

Alternatively, this may reflect a practical (rather than occupational health and safety) rationale for manufacturing MABs in a pharmacy clean room. Benefits of manufacturing in a pharmacy clean room include an ability to vial share (financial savings) and restriction of manufacturing to highly trained staff. Restricting manufacturing may theoretically reduce the risk of drug damage (MABs being sensitive proteinaceous compounds) or manufacturing error (e.g. wrong dose, volume or diluent) associated with incorrect handling and complex manipulations. Restriction of preparation to experienced or well-trained personnel (whether in a pharmacy clean room or not) has been demonstrated to reduce levels of microbial contamination in aseptically prepared parenteral medications.[27–29] This may provide additional motivation for centralised manufacturing. Survey results indicate that a combination of occupational health and safety and practical considerations were taken into account when deciding where MABs should be prepared.

The majority (99%) of clinicians believed that evidence of mutagenicity, teratogenicity or carcinogenicity of a drug in patients or healthcare workers was an important factor when considering appropriate

handling practices. This belief system aligns with current hazardous substance criteria.[1,2] However, it assumes first that this information is readily available and second, that there is a mechanism for internalisation (systemic bioavailability). Information relating to the toxicological profile of MABs is not as readily available as that of conventional medicines. As biotechnology-derived products, MABs are not subject to the same testing as conventional medicines. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, as pharmaceutical products derived from biotechnology, there is no requirement for MABs to be evaluated for either carcinogenicity or genotoxicity.[30] Although not formally tested for genotoxicity, mechanistically MABs do not directly interact with DNA (hence are not directly genotoxic). This point of view is agreed on by the American College of Toxicology and German Society of Toxicology, who state that there is little to no concern that bio-therapeutics may induce a genotoxic insult.[31] Furthermore, differing from traditional anticancer agents, MABs do not exhibit direct cytotoxic activity. They do however function as 'cytotoxic agents' with immune-mediated cytotoxicity or more specifically, antibody-dependent cellular cytotoxicity being a major mechanism of action.[32,33] The relevance of this indirect cytotoxic activity in regard to occupational exposure is unknown. However, as with other systemic effects, internalisation is the rate limiting step. The ability for MABs to be internalised by healthcare workers during routine occupational operations is unclear. NIOSH to date have justified exclusion of MABs from their hazardous substance register based on the belief that internalisation is improbable.[22] Accordingly, the common current practice of preparing MABs using full cytotoxic precautions is not supported by major occupational health and safety organisations.[1,2] A full review of available evidence, including pharmacologic principles and mechanistic internalisation evaluations for MABs, within the occupational setting, is required.

Comparison of clinician attitudes regarding the occupational exposure risks and hence required handling precautions for MABs demonstrated an overall trend (often reaching statistical significance) that nurses were more conservative and seeking greater guidance than pharmacists, who in turn were more conservative than medical staff. Practically, this may reflect the work-load of 'on the floor' nursing staff, who on the basis of time allocation alone may prefer not to manufacture/prepare agents. Differing attitudes among the professional groups are reflective of the level of potential exposure risk associated with each profession. Nursing staff are involved in both handling and administration (and sometimes preparation), pharmacy staff, only in the preparation and medical staff, either not at all or in the administration process only. This may also reflect differing knowledge and understandings of potential occupational exposure risks associated with MABs. Staff training and education relating to occupational health and safety risks is important for all disciplines. Results suggestive of a knowledge gap across all professions are that just 77/131 (45%) of all respondents (53% of nurses, 45% of pharmacists and 31% of doctors) considered the molecular size of MABs to be an important factor when considering exposure risk. The large molecular size of MABs, typically greater than 140 kDa, is orders of magnitude greater than traditional anticancer agents; molecular weight of gemcitabine is 299.66 Da.[34] More importantly, it is orders of magnitude greater than agents used for topical or transdermal drug delivery and of agents that are known contact allergens, which are typically less than 500 Da.[35] This strongly indicates that there is no pharmacologic mechanism for the dermal absorption of MABs.

A total of 46% of pharmacists compared with 61% of nurses strongly agreed that the complexity of manipulation and preparation is an important factor to consider in regard to the preparation of MABs. The processes involved in the preparation of these molecules are often complex, with numerous and multifaceted manipulations involved. A number of these drugs also have special instructions that need to be followed during the preparation process. For example, do not shake excessively, direct the stream of the diluent into or away from the powder in order to maintain integrity of the final product. Additionally, the calculations involved in determining the correct volumes of drug and diluent are often complex. The risk of error associated with preparation in a ward environment is not insignificant, with studies reporting frequencies of clinical interruptions at up to 5.2 interruptions/h of nursing medication preparation time.[36] In a busy ward environment, nursing staff may not have the time to prepare these drugs, particularly if complex processes are involved. Additionally, these agents may be used infrequently or use spread across multiple clinical areas of an individual institution and consequently staff may not be familiar with the processes involved.

The Australian Federal Government pays a compounding fee of $40 for the specialist requirements of preparing 'chemotherapy' medicine (currently bevacizumab, cetuximab, rituximab and trastuzumab receive funding in this manner).[37] This fee is paid regardless of whether reconstitution/manufacturing occurs in the pharmacy, by staff on the ward or by a third party

compounder. Attachment of a compounding fee therefore should not influence decisions regarding preparation of MABs. However, survey results indicate that this is an important consideration, with 68% of respondents citing PBS compounding fee payment as a determinant of manufacturing practices. Future research evaluating the economic impact of MAB (and other pharmaceuticals) handling practices would further inform policy in this area.

The results of this survey demonstrate that in the Australian healthcare setting, anticancer MABs are most commonly handled according to cytotoxic drug standards and most commonly in the absence of formal guidelines. Attitudes and beliefs of the occupational health and safety risk associated with these agents vary by profession and are divergent from the views of national and international occupational health and safety authorities. Respondents identified a need for guidelines for the handling of MABs. Concordantly, results from this survey were used to inform the development of Australian consensus guidelines for the safe handling of MABs for cancer treatment by healthcare personnel (available via the Western and Central Melbourne Integrated Cancer Services (WCMICS) website - http://www.wcmics.org/). Informed by the survey finding that both occupational and non-occupational health and safety issues were important factors to consider when determining how and where a MAB should be prepared, the developed guidelines recognise both considerations. Within the guidelines, in addition to definitive recommendations for the minimum safe handling requirements to protect healthcare personnel, a risk assessment model is also included to allow institutions to consider and evaluate clinical and operational (non-occupational health and safety) site-specific factors.

Declaration of Conflicting Interests

The following listed authors are consultants or advisory committee members or received honoraria, fees for service, or travel assistance (independent of research-related meetings) from or have research or other associations with the organizations listed: Michael Green – Roche and Sandoz; Sue Kirsa – Roche, Sandoz, Amgen, Orion, Perigo and Novartis and Senthil Lingaratnam – Roche and Sanofi-Aventis.

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