

**Guideline for the Preparation or Manipulation of Monoclonal Antibodies
(MABs) and related compounds such as Fusion Proteins, used in the
Treatment of Cancer**

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Changes Between Versions 1 and 2

Updated reference to drugs and to guidelines

1. Scope of guidelines

- 1.1 This document is written to provide the Network's position with regard to the preparation or manipulation of Monoclonal Antibodies (MABs) used in the treatment of cancer.
- 1.2 These recommendations exclude MABs intended for use in primary care vaccination programs, those produced by radio-pharmacy labs or those that come pre-formulated in a ready to use presentation.
- 1.3 This document is intended to cover monoclonal antibodies (MABs) or MAB derived products, including those conjugated to cytotoxic or small molecules directed against cancer cells. It does not cover other proteins and polypeptides, RNA or DNA based products. This document does not include reference to cell based therapies, vaccines or blood components.

2. Guideline background

- 2.1 The Breckenridge Report 1976¹ recommended that IV infusions should be prepared centrally in pharmacy under controlled conditions to ensure sterility and safety of the final injection. Although intended to apply to all infusional drugs the recommendations of the Breckenridge report have not been widely adopted within the NHS (other than in a few notable exceptions) for products other than cytotoxics and parenteral nutrition.
- 2.2 TPN preparation was taken into pharmacy because it requires multiple components, multiple calculations and is an ideal growth media for bacteria and cytotoxic preparation due to increasing concern for health of staff handling them. In February 2007 the National Patient Safety Agency (NPSA) has issued a safety alert for injectable medicines to address and expand on the issues originally raised by Breckenridge. This alert requires all drug preparation to be risk assessed and the identified risks managed appropriately. Preliminary examples of NPSA risk assessments focus on patient rather than staff safety and 'appropriate management' of the risks can be very subjective.
- 2.3 The assertion that Monoclonal Antibodies (MABs) are a special case in terms of risk and pharmacy or nurse manipulation is contentious as, in general, they require manipulation or calculation only marginally in excess of other ward-based preparations and handling hazards are unknown.
- 2.5 MABs can be raised for almost any biochemical or cellular target. Most of the targets for therapeutic MABs are present in healthy individuals. Some MABs lead to the death of targeted cells. However, they are not 'conventional' cytotoxic agents in that they do not directly or indirectly damage DNA or RNA, and therefore would not, as a class, be expected to be carcinogenic, mutagenic or teratogenic, in the patient themselves or in the staff handling the drugs. However there is the additional risk that the staff handling these agents could develop a risk of hypersensitivity to the agents or start to produce

neutralising antibodies against the proteins, whilst this second risk may not present an immediate clinical problem it could do so in the future if the individual need to receive the MAB in a therapeutic context.

- 2.6 In addition manufacturers have no formal data on the possible risks to staff of handling monoclonal antibodies predominantly because they are not required to provide this information for licensing purposes. Material Hazard Data Sheets (MHDS) or COSHH safety data sheets, which are a legal requirement, are available but tend to be geared towards industrial scale handling of raw material and are not easily translated to the clinical setting. Potential level of occupational exposure is difficult to quantify but some nurses have reported being able to taste MABs while reconstituting them, suggesting a low level of exposure.
- 2.7 As these drugs have only been in clinical use for a relatively short period of time, there is no in-use data on the risks of chronic low level exposure. The extrapolation of toxicity data obtained in therapeutic situations can be misleading.
- 2.8 There is increasing concern amongst chemotherapy nurses that relatively small numbers of predominantly female nurses of child bearing potential will be handling an increasing range of MABs and increasing numbers of doses over the coming years and that they are potentially receiving low level exposure or potentially exposing an unborn foetus to these agents. Damage to genetic material can be caused by very small amounts of drug. When insufficient to cause death of the cell, genetic damage may remain after the drug has disappeared from the system and may be carried through subsequent generations of cells contributing to the development of cancerous changes at some future time.
- 2.9 Cytotoxic drugs were not considered a handling hazard for many years until their mechanisms of action on genetic material were elucidated and epidemiological evidence emerged linking them to late adverse effects. Monoclonal antibodies acting at molecular level are new agents and their interactions with their cellular targets and the possible cascaded consequences of those interactions down to nuclear level are not clearly understood. It is therefore understandable that staff do not want to wait several years before any possible long term effects of MABs are seen and evidence to support safe handling strategies emerge.

3. Current national guidance

- 3.1 The lack of specific research in this area is acknowledged as is the pragmatic nature of existing guidance, in the absence of clinical sequel from exposure; the current national guidance and this local guidance is therefore based on an understanding of the chemical and pharmacological nature of the products involved, the potential theoretical risks based on our previous experience with 'conventional' cytotoxic drugs. Clearly any new product would need to be evaluated on an individual basis.

- 3.2 Current guidance states that therapeutic and experimental MAB's should ideally be prepared in pharmacy aseptic facilities in accordance with the Breckenridge Report 1976. However, it is recognised that this may not be practical. When pharmacy preparation does occur, existing aseptic facilities with appropriate product segregation may be used, dependant on the specific hazards of the individual product.
- 3.3 The Medicines and Healthcare Regulatory Agency (MHRA) have expressed dissatisfaction with the suggestion of using cytotoxic facilities for non-cytotoxic products in licensed units and may prohibit this activity.

Guideline statements

4. Summary of recommendations

- a) All MABs and structurally related compounds, such as fusion proteins, should be risk assessed using the NPSA risk assessment template.
 - b) Health and safety and safe handling issues in each individual handling area should have additional assessment.
 - c) The Health and Safety and Safe Handling assessments should be based on information obtained from Control of Substances Hazardous to Health (COSHH) data sheets, Material Hazard Data Sheets (MHDS), Summaries of Product Characteristics (SPC's), investigator brochures and other relevant information sources. Assessments should take into account the molecular and cellular level mechanism of action of each MAB as well as published toxicity data.
 - d) A decision on the action to take as a result of the risk assessment e.g. whether the identified risks of a particular agent in a particular setting are low enough to be considered insignificant or whether the implementation of risk reduction measures are cost effective, should be agreed at senior trust management level after consultation with staff groups involved.
- 4.1 Circumstances where pharmacy **must** prepare specific MABs (or buy them from 'Specials' manufacturers in ready to use form):
- MABs or MAB complexes with a) carcinogenic, mutagenic or teratogenic properties or b) potential to cause such effects based on the drug's action of causing damage to genetic or rapidly dividing material.
- 4.2 Circumstances where pharmacy **should** where possible prepare specific MABs (or buy them from 'Specials' manufacturers in ready to use form) unless there are significant practical or other constraints such as expiry or response time:
- MABs or MAB complexes with potential to cause unrelated to their therapeutic effect, damage to genetic material. There are several examples of such unrelated damage e.g. by suppressing the body's immune system allowing the development of cancer or by direct action on

foetal cells potentially causing deformity or abortion. MABs or MAB complexes requiring complex calculations or complex reconstitution techniques.

- MABs scoring red on NPSA scoring assessment in a particular area or under certain conditions e.g. areas where there is a lack of familiarity or lack of appropriate skill mix and where other possible means of risk reduction are insufficient or not feasible.
- MABs in trials requiring blinding of clinicians and nurses or where the trial protocol specifies pharmacy manipulation, or where the drug is so early in development that an evidence-based health and safety assessment is not possible.
- MABs where aseptic units are able to optimise potential for cost efficient use of drugs so as to achieve best value for money for Commissioners and the wider Health Economy within the constraints of Good Manufacturing Practice (GMP).

4.3. Trials

There are an increasing number of trials involving MABs in various stages of development from phase 1 to post licence. In some cases the protocols specify pharmacy manipulation but it is not always with any clear justification for that requirement. When challenged this stipulation is often removed but again with no clear justification other than to facilitate the trial's approval in the Trust. Some trials require blinding of the doctor and nurse which cannot be easily achieved without pharmacy manipulation. Other trials involve MABs in such early stages of development that very little data of any sort is available, let alone any data that could inform a safe handling debate.

- 4.4 As with all drugs, all MABs new to a particular area or staff group should also be assessed for education and training needs appropriate to the specific setting prior to their implementation as part of the overall risk reduction strategy.
- 4.5 Many of the concerns expressed by staff around MABs are based on lack of understanding of what these drugs are and how they work. As with any new drug brought into a clinical setting staff should make themselves familiar with the drugs and how they should be used and handled. MABs are not different in this respect. Education and training can be formal or informal, self directed, in house or Pharma Company coordinated.

5. Purchase of ready-to-use MABs

- 5.1 Some MABs are available for purchase from manufacturers in a ready-to-use form. Attention should be given to the stability and quality of these products especially when extended expiry dates are assigned or significant transport is necessary.

6. The use of closed system/safe transfer devices

- 6.1 Nurses preparing MABs in clinical areas should use Trust approved closed-system reconstitution/ safe transfer devices where these exist and are appropriate for the specific type of manipulation required.
- 6.2 There are an increasing number of devices coming onto the market that claim to provide a closed system method of reconstitution and transfer of IV drugs from vial to syringe or to infusion bag. All have benefits and limitations and none may be suitable in all circumstances. The use of these may remove or at least reduce the handling hazard concerns and may be especially useful where the handling concerns are contentious or where pharmacy manipulation is not feasible due to stability or practical issues. However, they may not address complexity or preparation issues raised by the NPSA assessments and may in some cases add to complexity and will require staff training in their safe and appropriate use. In addition the extra cost of these devices is not insignificant, would need to be considered, and would not necessarily be cheaper than aseptic preparation.

7. Summary of key points

- 7.1 Taking into account the issues above it is appropriate and sensible for pharmacy to supply MABs in a ready to use form wherever this is practical in order to reduce the handling at ward/clinic level and to address the NPSA patient safety concerns around complex calculations and reconstitutions. However there are some MABs that have to be made by pharmacy and others where a risk assessment and training are required if they are not to be made by pharmacy.
- 7.2 Each product has to be considered individually, NPSA risk assessment performed in conjunction with known toxicity data before a decision can be made as to whether the product should be made in pharmacy or not and if not made in pharmacy i.e. if bought in from a specials company, careful consideration should be given to expiry and stability of the products.
- 7.3 If agents have to be made at a ward or clinic level by non pharmacy staff then this must be in appropriate closed systems.

Monitoring of the guidance

Adherence to the Network guidelines may from time to time be formally monitored.

References

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