

# Assessing the risk of handling monoclonal antibodies

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- **OBJECTIVE** — To develop a risk assessment tool to inform healthcare staff about the risks associated with handling monoclonal antibodies (MABs) in a clinical setting.
- **METHODS** — A literature review was conducted. A health and safety risk assessment tool was devised for all MABs licensed in the UK, based on the origin of the MABs, their toxicities and a risk assessment as recommended by the National Patient Safety Agency.
- **RESULTS** — No specific data were found about the risks to healthcare staff from long-term exposure to MABs. The risk assessment tool identified two groups of MABs — those that should always be presented in a ready-to-use form sourced from pharmacy or commercial facilities, and those that may potentially be prepared in clinical areas.
- **CONCLUSION** — The risk assessment tool described in this paper may be used to aid decisions about which MABs can be prepared in clinical areas and which must be prepared in pharmacy facilities.

**M**onoclonal antibodies (MABs) were introduced into clinical therapeutic practice in 1986.<sup>1</sup> There are currently 16 MAB products licensed for therapeutic use in the UK. Guidance to the NHS on the handling of MABs was first published in 2001. The most current version emphasises the proteinaceous nature of these products and their potential to cause sensitisation to healthcare staff.<sup>2</sup> It gives general guidance on observing good aseptic compounding practice and preventing cross-contamination in pharmacy compounding facilities.

Hospital pharmacists and nurses at the University Hospital of North Staffordshire have had concerns for some time about the safety aspects of handling MABs, given the profound action of MABs at the cellular level. This concern is exacerbated by a general lack of understanding of the risks associated with protein therapeutics. There does not appear to be any published information on the potential risks to healthcare staff from low grade exposure to MABs over long periods. In view of this, a review of the current literature was undertaken, and a risk assessment tool was developed, to inform healthcare staff of potential risks and offer guidance on safe handling in the clinical setting.

## Method

An extensive information search was undertaken using the following sources:

- Medical databases including Embase and Medline
- The internet
- Summary of product characteristics datasheets for each MAB
- Health and safety datasheets, where available

A health and safety risk assessment tool for MABs was devised from the information obtained, as described below.

The health and safety assessment examined the allergic potential based on the origin of the MAB. There are three types of MAB product, those of completely murine origin (mouse or hamster protein; suffix “momab” or “mumab”); partially humanised (chimeric, suffix “ximab”) or 75 per cent

humanised (suffix “zumab”). A numerical score from 1 to 3 was assigned according to the content of foreign protein in the product; 3 for murine, 2 for chimeric and 1 for fully humanised.

Toxicities arising from the therapeutic use of MABs were assessed using toxicity warnings from the summary of product characteristics datasheets, published toxicity warnings<sup>3</sup> and health and safety datasheets, where available. The toxicity data was scored from 1 to 4 as follows:

- 1=Potential to cause adverse events (eg, unmasking of latent conditions such as tuberculosis)
- 2=Associated with well defined but rare toxic symptoms
- 3=A well established risk of toxicity
- 4=Known or potential cytotoxic, teratogenic or embryotoxic properties, risk of initiating a cancer or possessing radioactive properties

The above scores were added together to give a health and safety risk assessment as below:

- < 3 = low risk
- 3 to 5 = moderate risk
- 6 and above = high risk

A risk assessment for the preparation of intravenous medicines, as recommended by the National Patient Safety Agency,<sup>4</sup> was then undertaken for each MAB.

The risks from both the health and safety assessment and the NPSA assessment were combined to establish the overall risk for each individual MAB. In principle, this has the benefit of balancing the risks from preparation and presentation covered by the

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NPSA approach, with safety factors. Overall risk factors were determined as follows:

- Any combination of high risk (health and safety high risk *or* NPSA “red” risk rating) = high risk
- Moderate *plus* moderate (health and safety moderate risk *plus* NPSA “amber” risk rating) = moderate risk
- Moderate *plus* low (health and safety moderate risk *plus* NPSA “green” risk rating) = low moderate risk
- Low *plus* moderate (health and safety low risk *plus* NPSA “amber” risk rating) = low moderate risk
- Low *plus* low (health and safety low risk *plus* NPSA “green” risk rating) = low risk

The overall risk could then be used to inform a decision for compounding the MAB within pharmacy facilities (for products with a high to moderate risk) or, in the event of capacity and other constraints, permit preparation in a clinical area (low or low moderate risk products).

## Results

Despite an extensive literature search, no specific data relating to the risks to healthcare staff from chronic low grade exposure to MABs were found.

The health and safety risk assessment is shown in Table 1. This assessment, combined with the NPSA risk assessment, gives the combined risk assessment shown in Table 2 (p62). From these data, two categories of MABs have been identified — those that represent a relatively low risk to healthcare staff and may potentially be prepared in clinical areas, and a high risk

category that should always be presented in a ready-to-use form sourced from pharmacy or commercial facilities. This is shown in Table 3 (p64).

## Discussion

The potential for adverse effects to healthcare staff from the handling of medicinal products has been well established for cancer chemotherapy. With the introduction of MABs, many of which are used in the treatment of cancer, it was inevitable that questions regarding their safe handling would be raised.

The adverse effects of MABs arise from their potential to cause allergic and immunogenic reactions. Developments in technology have seen the murine protein component in MABs successively reduced to about 30 per cent for chimeric MABs<sup>5</sup> and to 25 per cent or less in “zumabs”, thus informing our initial health and safety scoring.

In principle, the therapeutic attractiveness and safety of MABs arises from their potential for highly specific interactions with well defined antigens, limiting the capacity for unpredictable toxicities and side effects.<sup>6</sup> However, despite the apparent specificity of MABs, absolute antigen specificity is rarely obtained in practice.<sup>7,8</sup> Furthermore, MABs can have unforeseen adverse effects and fully engineered human proteins can be immunogenic.<sup>9</sup>

The potential toxicities of MABs include the following:<sup>9-11</sup>

- Formation of neutralising antibodies, which may be of no clinical significance, but may provoke allergy, anaphylaxis or serum sickness

- Loss of clinical response
- Cross-reaction with endogenous protein(s) with vital biological function
- Enhancement of immune system activity leading to cytokine storm and, in severe cases, systemic inflammatory response syndrome.

The above toxicities arise from both product and patient factors. For example, in immunocompromised patients an immunogenic response may not be of clinical significance, but the effect could be different in an immunocompetent member of staff.

With regard to product formulation in protein therapeutics, the most extreme example to date has been with changes to the formulation and packaging of erythropoietin. This led to the formation of immunogenic products and consequently to pure red cell aplasia in some renal patients. With the patent expiry on first-generation MAB products approaching, the development of “biosimilars”, where far greater variability is inherent in product development than is the case with traditional generic medicinal products, changes in toxicity profiles may be expected.<sup>10,11</sup>

The tragic events from the phase I trial with TGN1412 highlight the unforeseen toxicity that can arise from the enhancement of immune function, in this case in the form of a cytokine storm.<sup>12,13</sup> This syndrome has also been observed to a less severe degree with OKT3, alemtuzumab and rituximab.<sup>14</sup> In addition, the rapid onset of injury to the lung in response to TGN1412 suggested an immune-mediated injury specific to the lung.<sup>15</sup> The difficulties involved in preclinical testing and the shortcomings of existing test methods in the prediction of

Table 1: Health and safety risk assessment for monoclonal antibody products

Approved name	Relative antigenicity	Score	Significant toxicity from SPCs and FDA warning <sup>3</sup>	Score	Total score	Health and safety risk
Abciximab (c)	Moderate	2	Low toxicity	0	2	Low
Adalimumab (m)	High	3	Unmasks tuberculosis	1	4	Moderate
Alemtuzumab (h)	Low	1	Pregnant staff should not handle	4	5	Moderate
Basiliximab (c)	Moderate	2	Rare incidence of significant toxicity	2	4	Moderate
Bevacizumab (c)	Moderate	2	Possibly embryotoxic and teratogenic	4	6	High
Cetuximab (c)	Moderate	2	Rare incidence of significant toxicity	2	4	Moderate
Daclizumab (h)	Low	1	Possible increased abortion rate	4	5	Moderate
Efalizumab (h)	Low	1	Low toxicity	0	1	Low
Gemtuzumab (h)	Low	1	Cytotoxic	4	5	Moderate
Infliximab (c)	Moderate	2	Low toxicity	0	2	Low
Omalizumab (h)	Low	1	Possible cancer risk	4	5	Moderate
Palivizumab (h)	Low	1	Rare incidence of significant toxicity	2	3	Moderate
Rituximab (c)	Moderate	2	Significant toxicity	3	5	Moderate
Tositumomab (m)	High	3	Radioactive	4	7	High
Trastuzumab (h)	Low	1	Low toxicity	0	1	Low
Ibritumomab-tiuxetan (m)	High	3	Radioactive	4	7	High

c = chimeric, m = murine, h = humanised

Table 2: Combined National Patient Safety Agency<sup>3</sup> and health and safety risk assessment

Approved name	Therapeutic risk	Concentrate	Complicated calculation	Complicated method	Reconstitute vial	Part vial	Pump	Non-standard infusion set	NPSA risk	Health and safety risk	Overall risk
Abciximab	N	Y	Y	Y	N	Y	Y	Y	High	Low	High
Adalimumab	Y	N	N	N	N	N	N	N	Low	Moderate	Low / moderate
Alemtuzumab	Y	Y	Y	Y	N	Y	Y	N	High	Moderate	High
Basiliximab	Y	N	N	N	Y	N	Y	N	Low	Moderate	Low / moderate
Bevacizumab	Y	Y	N	Y	N	Y	Y	N	Moderate	High	High
Cetuximab	Y	Y	N	Y	N	Y	Y	Y	High	Moderate	High
Daclizumab	Y	N	N	Y	N	Y	N	N	Low	Moderate	Low / moderate
Efalizumab	N	N	N	N	Y	Y	N	N	Low	Low	Low
Gemtuzumab	Y	Y	Y	Y	Y	Y	Y	N	High	Moderate	High
Infliximab	Y	Y	N	Y	Y	Y	Y	N	High	Low	High
Omalizumab	Y	N	Y	Y	Y	Y	N	N	Moderate	Moderate	Moderate
Palivizumab	Y	N	N	N	Y	Y	N	N	Low	Moderate	Low / moderate
Rituximab	Y	Y	N	Y	N	Y	Y	N	Moderate	Moderate	Moderate
Tositumomab	Y	Y	Y	Y	N	Y	Y	Y	High	High	High
Trastuzumab	Y	Y	Y	Y	Y	Y	Y	N	High	Low	High
Ibritumomab -tiuxetan	Y	Y	Y	Y	Y	Y	N	Y	High	High	High

immunogenicity are discussed in many of the papers reviewed for this exercise.<sup>9-12</sup> The report from the expert group on phase I clinical trials<sup>12</sup>, set up following the TGN1412 incident, concluded: "It is now apparent that the pre-clinical development of such agents cannot rely on methods that served well with smaller chemical molecules or previous generations of biological medicines".

The risks to healthcare staff from long-term, low-grade exposure to potentially toxic medicines arise mainly from the inhalation of aerosols formed during preparation and administration and possible surface contamination. In the absence of any published studies, the present risk assessment from the long-term exposure to MABs has to be extrapolated from data relating to their therapeutic use (Table 2). Although this involves doses to which healthcare staff would not normally be exposed, it should be noted that allergic and immunogenic reactions may not require exposure to therapeutic doses.

Given the available evidence, we suggest the following points:

- Long-term, low-grade exposure may lead to the formation of antibodies which could cause allergic reactions of varying severity
- Antibodies developed at work could adversely affect subsequent treatment of staff if they were to develop conditions requiring therapeutic treatment
- Exposure to agents provoking cytokine release, particularly if this involves lung-mediated inflammatory mechanisms, must be a concern

- Some MABs are associated with well-established cytotoxic risks and other high risks

The formation of antibodies to MABs could form the basis for occupational health screening of staff exposure to these products.

Information contained in the health and safety datasheets examined was variable and did not add to the information obtained from other sources. As with preclinical testing, the test methods and toxicity classifications based on small molecule chemistry may not be suitable for assessing the risks posed by MABs and other protein-based therapeutic substances.

Because the health and safety risk assessment had to be based on the therapeutic toxicities of MABs, this invariably informed the response to the "therapeutic risk" section of the NPSA risk assessment. This has resulted in a variance between the risk assigned to two MABs (infliximab and trastuzumab) in the draft example risk assessment published by the NPSA, and the risk assigned by us. Infliximab and trastuzumab both scored low on the health and safety risk and, in our view, could be prepared in clinical areas if need be.

The NPSA risk assessment is understandably weighted towards preparation and presentation of intravenous medicines, but the definition of "therapeutic risk" appears to be wide ranging and possibly subjective. Moreover, while it is desirable that all intravenous products should be prepared for use in pharmacy facilities, account has to be taken of available local capacity, the short

shelf-life of some MABs following reconstitution and the need for rapid clinical response (eg, in the use of Abciximab).

## Conclusion

The potential risks from handling MABs have been reviewed. Based on information currently available, MABs can be split into two groups — the first posing relatively low handling risks, that may permit preparation in clinical areas, and a second group for which handling in pharmaceutical isolation facilities would be advisable. The risk assessment approach described in this paper will aid decisions about which products must be prepared in pharmacy and which may be prepared in a clinical area. It should be emphasised that preparation in clinical areas must still be conducted using protective face masks, gloves, armlets and aprons. In addition, good aseptic practice that includes techniques for minimising the formation of aerosols and maintaining the sterility of product for administration must be followed.

In 2004, over 400 biotechnology pharmaceuticals were in development.<sup>11</sup> Issues raised regarding handling of these products will become an increasingly important issue for healthcare staff. Unfortunately, long-term occupational exposure does not appear to be given enough attention in pharmaceutical product development at present. Current methods of assessing health and safety risks posed by protein pharmaceuticals are inadequate.

See p64 for Table 3 and references

**Table 3: Recommended list of monoclonal antibody products for preparation in clinical areas or pharmacy facilities**

<b>May be prepared in clinical areas (low to low/moderate risk)</b>	<b>Should be prepared in pharmacy facilities and presented in a ready-to-use form (high to moderate risk)</b>
Adalimumab (Humira) Basiliximab (Simulet) Daclizumab (Zenepax) Efalizumab (Raptiva) Palivizumab (Synagis)	Abciximab (Reopro) Alemtuzumab (Mabcampath) Bevacizumab (Avastin) Cetuximab (Erbix) Gemtuzumab (Mylotarg) Infliximab (Remicade)* Omalizumab (Xolair) Rituximab (MabThera) Tositumomab and iodine 131 (Bexxar) Trastuzumab (Herceptin)* Ibritumomab tiuxetan (In-111 or Y-90) (Zevalin)

\*May be prepared in clinical areas if needed (see discussion, p62)

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