By Gareth Malson, MRPharmS

These days, all intravenous, cytotoxic drugs are prepared in aseptic manufacturing units. So they should be. After all, how many nurses would want to risk their personal health by preparing such medicines themselves? The same practice is not routine when preparing monoclonal antibodies (MABs), despite the fact they are potent biopharmaceuticals that interact with cells and, in the case of several medicines, cause cell death. Is this reasonable?

Views were mixed at a recent "Management and awareness of risks of cytotoxic handling" (MARCH) conference, held in London on 16 June. At the event, the following motion was debated: "Monoclonal antibodies and other targeted therapies should be treated as cytotoxic drugs during preparation, administration and disposal until it can be shown that they do not pose an occupational hazard to staff."

Arguing for the motion was Andrew Stanley, lead pharmacist, Pan-Birmingham Cancer Network. Arguing against was Annie Young, acting network director, 3 Counties Cancer Network.

Avoid repeating mistakes

"Once upon a time, a clever scientist worked out why people's blood counts had dropped after exposure to mustine gas during the First World War. A far cleverer mind than mine works out that this has therapeutic advantages," began Mr Stanley. "This led to the development of cancer chemotherapy." He was basing his argument on a comparison between what is known now about MABs and what was known in the early 1960s about cytotoxic drugs.

"As with all things in life, there's no such thing as a free lunch," he pronounced. "Sadly, we were to find out that this monumental step forward in medical treatment was to be accompanied by some unfortunate consequences."

In the early days of cancer chemotherapy treatment, he explained, medicines were prepared without due care. The implications of this practice were not understood until the first cases of malignancy due to occupational exposure to chemotherapy were detected: "It took us from exposure in the 1960s until the late 1970s to understand the damage we had done."

Due care has now been built into the preparation of cytotoxic medicines. "We now know we got it right with the introduction of aseptic production of chemotherapy," Mr Stanley told the audience. "Nobody would now want to make up routine chemotherapy on the wards."

He turned his focus to MABs. "Undeniably, they work," he said. "They are altering the clinical course of cancer day-in, day-out. That is fact. But does this not sound familiar to the story we heard [about chemotherapy]?

Mr Stanley believes that the possibility of biological medicines being harmful to healthy cells cannot be ruled out. He offered trastuzumab as an example: although the drug's target, the HER2 receptor, is expressed in breast cancer tissue, it is also expressed on cardiac muscle. "I cannot prove what low-level exposure and blockade of your HER2 receptor will mean," he said, and speculated that, if cardiac effects were to occur in staff who have handled the drug, these might not become apparent for 20 years.

He also spoke about MABs that interact with tumour necrosis factor (TNF). It is known that TNF is overproduced in patients with rheumatoid arthritis, so MABs are used to downregulate its level. However, the consequences of unintentionally reducing normal levels of TNF through occupational exposure to anti-TNF MABs are not known, he argued.

Ms Young rebutted Mr Stanley's arguments by pointing out that traditional chemotherapy and MABs act differently. Chemotherapy acts on all dividing cells, normal and malignant, she explained, whereas MABs only affect the cells that carry the targeted antigen. After binding, they activate the host immune system and trigger cell lysis. "They do not directly interact with the..."
transcription of DNA and RNA,” she added, “and would not be expected to be mutagenic or teratogenic.”

Further justification for rejecting the motion comes from dermatologists, Ms Young added, who work according to the “500 Dalton rule”. The rule suggests that any compound over 500 Daltons in size is too large to penetrate the skin. MABs measure in the magnitude of 10^5 Daltons, she pointed out, “therefore they resist penetration, do not act as allergens and are washed off the skin”.

Evidence scanty
Ms Young reckons the motion is unnecessarily cautious: “Any evidence that monoclonal antibodies need to be handled as cytotoxic therapies is scanty at best.” One key research paper supporting the motion, a risk assessment tool for MABs known as the “Langford paper”, was published in *Hospital Pharmacist* last year (2008;15:60). However, Ms Young questioned the methodology of the research and pointed out that its results had been criticised by several pharmaceutical company representatives for classifying too many MABs as “high risk” (*Hospital Pharmacist* 2008;15:138 and 2008;15:257).

Capacity was also raised as an issue. Ms Young does not believe many hospital pharmacy departments are in the position to take on additional preparative services. Most district general hospitals are currently forced to prioritise which products they can prepare in the pharmacy, she stressed, adding: “We are still a long way from fulfilling the Breckenridge report [published by the Department of Health in 1976], which said that all intravenous drugs should be prepared centrally.”

She argued that a sensible approach should prevail and that nurses, as “intelligent, lateral thinkers”, should be trusted to judge what they are comfortable doing. This was a position backed by several expert groups, she said. For example, the United Kingdom Oncology Nursing Society suggests that clinicians should use common sense when handling MABs and avoid unnecessary exposure. It advocates the use of personal protective clothing (eg, gloves, aprons, goggles) but does not suggest the preparation of MABs in clinical or ward areas should be avoided.

In addition, she highlighted a policy document from the British Oncology Pharmacy Association, which said that medium- to low-risk products could be prepared in clinical areas (however, she noted that the document did not specify how a risk assessment should be carried out).

How cautious?
Evidently, your views on the level of caution needed when handling MABs will determine which side of the fence you stand on. Mr Stanley sought to convince the audience to err on the side of caution. Because the effect of low-level occupational exposure to MABs and other biological treatments is not known, the only safe option is to insist on all such therapies being prepared in aseptic manufacturing units, he made clear. That way, the mistakes made from handling cytotoxics during the 1960s would not be repeated, he said.

Ms Young recalled the words of Max Summerhayes, a founding member of BOPA, who said: “Any system that is overcautious and exaggerates the risk of low hazard products may result in displacing those products that represent a greater risk to patients from central preparation.”

She wrapped up: “Oncology nursing bodies don’t support the case, oncology pharmacy bodies don’t support the case, . . . we have no credible risk assessment tool, NHS pharmacy departments do not have the capacity to prepare all agents on the market, as well as those in development, and patients suffer [from lengthy waiting times].”

Following the debate, Graham Sewell, chairman of the MARCH panel, shared a case report of which he had recently been made aware. A nurse at Royal Darwin Hospital, Australia, had become sensitised to trastuzumab as a result of occupational exposure and gone on to develop “full-blown anaphylaxis”. This, he said, highlighted how little we know about these new types of treatment.