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### External Contamination of Cytotoxic Drug Vials

On the basis of clinical and laboratory studies, many cytotoxic drugs have been found to be mutagenic, teratogenic and carcinogenic.<sup>1,2</sup> Patients receiving therapeutic doses of these drugs are subject to a number of acute and chronic adverse effects. Occupational exposure to cytotoxic drugs has been recognised as a potential health hazard to those involved in their preparation and administration for over 25 years.<sup>3</sup> The implementation of a variety of safe handling techniques, especially cytotoxic drug safety cabinets, has dramatically reduced the risk of exposure. Nevertheless, substantial levels of contamination from cytotoxic drugs have been detected on surfaces in drug preparation and administration areas, despite the use of recommended safety equipment.<sup>4</sup> Although the risk associated with low-level exposure has yet to be determined, it is assumed to be present and has resulted in the development of numerous guidelines for the safe handling of cytotoxic drugs.

The risk to healthcare workers has generally been assumed to be limited to those directly involved in the preparation (pharmacists, technicians) and administration (nurses) of cytotoxic drugs. However, recent studies have demonstrated that the outer surface of vials can be contaminated with the cytotoxic drug contained within the vial.<sup>5-11</sup> This places employees, such as store personnel or other non-technical staff, who may be involved in packing and unpacking or placing stock on shelves, at risk of exposure. These staff would not routinely be wearing any type of protective equipment.

In 1997, a Dutch study found significant contamination on the outside of cyclophosphamide drug vials.<sup>5</sup> Delporte et al. showed that primary packaging of different batches of fluorouracil (5-FU) available in Belgium were contaminated.<sup>6</sup> The frequency and level of drug residue found varied depending on the manufacturer. Platinum-containing drugs from three manufacturers tested in a Swedish study showed that vials may already be contaminated on the outside when delivered from the manufacturer.<sup>7</sup> Following the detection of low-level contamination on the floor surfaces and disposable gloves

worn by staff in two UK hospital pharmacy departments using isolators, Mason et al. investigated the level of cytotoxic drug contamination on the external surfaces of the vials as delivered to the hospital pharmacy stores.<sup>8</sup> They tested vials containing carboplatin, cisplatin, cyclophosphamide, ifosfamide and methotrexate and found that a significant number of vials had a quantifiable level of external contamination. A French study measured the external contamination on cyclophosphamide, docetaxel, doxorubicin, etoposide, 5-FU and ifosfamide vials.<sup>9</sup> All vials tested were contaminated though levels varied depending on the supplier. The outer packaging containing the 5-FU vials was also contaminated but no contamination was detected on the plastic packaging of etoposide.

Connor et al. reported the results of three studies undertaken in the USA and Europe.<sup>10</sup> The first study evaluated the external contamination of vials with ifosfamide and cyclophosphamide and found widespread contamination with each drug. Cyclophosphamide and 5-FU surface contamination was examined in three pharmacies in the second study. Cyclophosphamide was found on the exterior of most vials while sporadic contamination was detected with 5-FU, possibly due to a less sensitive assay. In the final study, reduction in the amount of external cisplatin contamination was investigated using different decontamination procedures. A small Canadian study has also detected contamination of the external surface of cyclophosphamide vials.<sup>11</sup>

What strategies have been implemented by the pharmaceutical industry in Australia to limit the possible external contamination of cytotoxic vials? On behalf of The Society of Hospital Pharmacists of Australia's (SHPA) Committee of Specialty Practice in Oncology, a letter was sent to all pharmaceutical companies who supply parenteral cytotoxic drugs to the Australian market. The letter briefly outlined the data concerning the potential for contamination from the outer surface of cytotoxic drug vials and the possible risks this poses to staff handling these vials. It requested information detailing what procedures had been instituted to ensure that their products were not externally contaminated.

Replies were received from all 20 companies providing parenteral cytotoxics. Three companies are no longer supplying cytotoxic drugs in Australia or will cease supply when current stocks are exhausted. Most of the remaining companies (12/17) use some form of decontamination involving an external washing of vials with water. A validated decontamination process was cited by four companies, but others appeared to depend solely on visual inspection. Five companies rely solely on a system of visual inspection and rejection of contaminated vials. One of these companies is currently constructing a new plant that will include an external washing process for vials. Most companies advised the use of gloves when handling cytotoxic drug vials. Several companies provided data on their strategies to prevent accidental breakage of vials during transportation and handling.

Many companies appeared to be unaware of this important issue. Hence, the required data was not on hand and had to be obtained from overseas through the actual manufacturers of the product. Despite modern communication systems, this often took an unnecessarily long time. The level of information received from companies varied, with some companies providing detailed information on the processes used and others only limited data. To maintain confidentiality, information

has been de-identified. It is important to acknowledge the efforts of all pharmaceutical companies in responding and we look forward to continuing to work together to improve this safety issue in Australia.

The number of studies that have investigated contamination on the external surfaces of cytotoxic drug vials is small.<sup>5-11</sup> These studies have only examined a limited number of drugs and a small quantity of vials from each product. No studies have been conducted on drugs distributed in Australia. For definitive data, all batches of all cytotoxic drugs from all manufacturers would need to be tested. Despite this, there is sufficient data to raise concerns. If unprotected hands are used to remove the outer packaging of cytotoxic drugs or touch vials when preparing for manipulation, staff are likely to come into contact with contaminated surfaces and absorb potentially harmful quantities of these hazardous drugs.

Due to the availability of a sensitive analytical technique, cisplatin was used to test a number of different decontamination methods.<sup>10</sup> Vials were tested following a standard decontamination procedure used until 2002, an improved process involving a vial washer, and vials washed under the improved process that had the additional protection of sleeves tightly shrunk around the vials. Reductions in the surface contamination of vials were seen with the improved decontamination process and this was further reduced with the addition of sleeve protection to vials, though not completely eliminated. Therefore, effective techniques are available for manufacturers to implement that will assist in the reduction of external contamination of vials. Individual companies may have since developed further advanced techniques.

Luci Power has urged pharmacists, as the purchasers of drugs, to demand clean vials.<sup>12</sup> She states that we must tell distributors, manufacturers, purchasing groups, professional societies, and all other pertinent parties that we are aware of this contamination and that it is unacceptable. Purchasers should include vial cleanliness as a selection criteria for stock purchase and buy from only those manufacturers who provide clean vials.<sup>12</sup> SHPA recommends that all personnel involved in the receipt, distribution and storage of cytotoxic drugs must receive appropriate instruction on their hazards and training in the correct procedures for dealing with breakages and spills.<sup>2</sup> They suggest that consideration be given to preferentially purchasing products that can be packaged in such a way to minimise the chance of breakage.

Manufacturers and suppliers of cytotoxic drugs appear to have a moral and possibly legal obligation to ensure that their products are safe and without risk when used properly. Appropriate control measures must be in place to ensure that there is no cytotoxic residue contaminating the outside of the primary container or other packaging which would pose a risk to workers handling the product at various points in the supply chain. Some companies have taken this responsibility very seriously and provided excellent safeguards. However, until all companies adopt decontamination processes to ensure totally clean vials and use packaging that guarantees that breakage during transportation is eliminated, we must insist on stringent occupational safety programs. Persons involved in the drug distribution, receiving, packing or unpacking, storage and inventory control must wear protective gloves whenever handling drug vials or outer packaging. If the outer surface of vials are contaminated, it is also likely that the inside of the carton or wrap and any package

insert is also contaminated.<sup>12</sup> Cytotoxic drugs should be clearly identified on the external packaging or boxes so that staff know when to use protective equipment. All contaminated materials must be handled with appropriate protection and disposed of as for cytotoxic waste. Material safety data sheets and package inserts for all cytotoxic drugs should detail what decontamination procedures have been used to ensure clean vials. Information should also include whether decontamination procedures are validated and to what level of contamination vials are guaranteed. The importance of always wearing protective gloves when handling cytotoxic drugs and associated packaging should be clearly stated.

Pharmacists must pressurise pharmaceutical companies to take measures to minimise the contamination of any packaging and to reduce the risk of breakage during transportation. Internal precautions must be taken in pharmacy departments to ensure that personnel engaged in receipting of deliveries, unpacking or packing of stock, placing stock in storage areas or getting medications ready for manufacture, are aware of the potential risks involved. These staff must receive appropriate training in safe handling including the need to wear gloves when handling these products and the procedures to follow should breakages occur.

It is clear that there is a leadership role for SHPA in continuing to promote safe handling guidelines, working with directors of pharmacy to improve staff training and with the pharmaceutical industry to reduce the risks, consistent with the partnership approach of Australia's National Medicines Policy.

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