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# Safe handling of cytotoxics

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# Safe preparation and administration of cytotoxics

A European Pharmacy Expert Panel concluded that new products and new working methods are needed to ensure safe handling of cytotoxic drugs

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***Hospital Pharmacy Europe* recently** hosted a meeting of a panel of European expert pharmacists in Frankfurt, Germany to review the safe preparation and administration of cytotoxic drugs. Topics included hazards of cytotoxic drug preparation, safety assurance requirements and the likely impact of the European Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. Participants also had the opportunity to examine a number of devices.

In order to set the scene, each participant gave a short presentation on the preparation of cytotoxic drugs in their hospitals. Centralised pharmacy cytotoxic preparation services were operated by all hospitals represented. All countries supported the principle of providing as many injections as possible in ready-to-use (RTU) or ready-to-administer (RTA) form, although in practice this is sometimes difficult to achieve. One aim of the Spanish hospital pharmacy society's '2020 initiative' is for 100% of hospitals to be dispensing intravenous doses in a RTU or RTA form by 2020. The presentations showed that European countries have much in common but there are local variations.

## Occupational exposure

Occupational exposure of healthcare workers to cytotoxic drugs was an issue that concerned all pharmacists. The need to protect pharmacy personnel, ward staff and others who might come into contact with cytotoxic drugs was recognised by all participants.

In order to minimise contamination of the working area and reduce the likelihood of occupational exposure of pharmacy personnel, pharmacy technicians prepare cytotoxic doses in vertical laminar flow cabinets or isolators. They often use reconstitution spikes rather than needles to minimise leakage of droplets or aerosols of the drug solutions. Other important measures include frequent changes of the work surface protective cover, regular changes of gloves and the use of validated cleaning processes. All these measures are required to minimise contamination of the working area with cytotoxic drugs.

Dermal exposure is an important route of contamination for personnel involved in preparation of cytotoxic doses and 'double-gloving' is important to minimise the chances of skin coming into contact with contaminated surfaces.

Some researchers have investigated the extent of contamination with cytotoxic drugs in the preparation areas of pharmacies, using highly sensitive techniques that can detect picogram quantities of cytotoxic drugs. Measurements made in Danish hospital pharmacies have shown that environmental contamination with cyclophosphamide and ifosfamide has fallen to very low levels over a seven-year period. It is of interest that this has been achieved without the use of closed system transfer devices (CSTDs). Training of operators in good cytotoxic drug handling technique and correct use of all devices is probably the most important factor in minimising local contamination.

## Closed systems

Closed system transfer devices are advocated to minimise leakage of

## Case study

### Safety improvements in the preparation of intravenous cytotoxic drugs

The first evidence of occupational exposure of health care workers to cytotoxic agents was published by Falck in 1979, and since then there have been numerous publications dealing with this topic, said **Bertrand Favier** (Production Pharmacist, Cancer Hospital Lyon, France), describing how practices have been developed to improve the safety of intravenous drugs for use in oncology.

The first step was to determine where and how environmental contamination arose and this was done using fluorescein to detect leakage or spillage during compounding. The results showed that the most commonly contaminated areas were the work surface cover and the gloves. There were also splashes on the walls of the cabinet. Procedures were altered such that the work surface cover and gloves were changed more frequently and vented needles were introduced to avoid overpressure.

A further study to examine the contamination of gloves during preparation showed that there was considerable variability between operators – some staff contaminated their gloves on relatively few occasions but one contaminated the gloves on 100% of occasions. Procedures were changed to ensure that air was only expelled from syringes with a cap over the needle and staff training was reviewed. The training and education of staff in good techniques was critical, noted Dr Favier.

The most dramatic results were seen when the impact of priming the administration sets in the pharmacy was investigated. A study compared the levels of 5-fluorouracil (5-FU) on nurses' gloves when pharmacy-primed administration sets were used and when the administration sets were attached and primed on the ward. The results showed that the risk of contamination was doubled and the amount of 5-FU on the gloves was increased eight-fold when the administration sets were attached and primed on the ward. Consequently, administration sets are now attached and primed in the pharmacy. This study also underlined the need for a proper quality assurance procedure for administration of cytotoxic agents, commented Dr Favier.

A comparison between laminar flow cabinets and isolators had shown that levels of contamination were higher in isolators than in laminar flow cabinets. These results had prompted Dr Favier to keep laminar flow cabinets in his department.

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cytotoxic drugs. There was uncertainty about the precise definitions of open and closed systems. Some pharmacists referred to the definitions given in official guidelines whilst others felt that vials are, in their very nature, closed systems. The panel agreed that chemical and microbiological closed systems need to be defined clearly.

The National Institute for Occupational Safety and Health (NIOSH) defines a closed system as "a device that does not exchange unfiltered air or contaminants with the adjacent environment". This closed system definition originally referred to a biological safety cabinet and not to drug containment devices. A drug containment device is one that is both airtight and leakproof. NIOSH defines a closed system drug transfer device as "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system".

Some centres use CSTDs routinely in the preparation of cytotoxic injections but others do not. In one hospital in France, in order to protect healthcare workers from occupational exposure to methotrexate a CSTD (BD-PhaSeal) is provided for nurses to make up methotrexate injection on the ward (for urgent treatment of ectopic pregnancy).

One hospital has found that one CSTD (BD-PhaSeal) requires approximately seven times extra force to be applied (compared with a simple needle) and therefore increases the risk of repetitive strain injury (RSI).

### Robotic preparation

Another approach to containment of cytotoxic drugs has been the use of compounding robots to prepare doses. This is most widespread in Turkey, where 35 hospitals are using robotic systems, including 12 hospitals that use a total of 14 Cytocare robots. Cytocare robots can prepare cytotoxic injections in sterile conditions once the ingredients have been placed in the robot cabinet and the details entered into the robot's computer. Smaller numbers of Cytocare robots are also in use in the Czech Republic, Denmark, Italy and Spain.

One key advantage of the Cytocare robot is that, when correctly adjusted, it can prepare cytotoxic doses with no spillage at all. In addition, it is possible to organise the pharmacy workload so that a compounding robot is used for the jobs that it handles best, leaving pharmacy staff free to prepare other products.

At present there are a number of disadvantages to the use of compounding robots. Current robotic compounding systems are expensive and slow – one is able to make only 35 injections in eight hours. The speed of operation is also dependent on the altitude at which the robot is situated. Compounding robots

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can only work with one type of transfer device – this is, in effect, a fixed combination. Finally, the software of the compounding robot does not interface with other pharmacy software and users reported that additional staff are needed to support compounding robots.

## Pharmaceutical aspects

In the UK and France, positive pressure isolators are widely used for cytotoxic preparation. The isolators are regularly cleaned and tested to ensure that they are functioning correctly.

There was general agreement that products should be wiped (rather than sprayed) when they are transferred in or out of the cabinet or isolator to ensure effective disinfection and decontamination. There was also general agreement that double-gloving is required and that there should be frequent changes of gloves, although the intervals varied from 15 minutes to two hours.

'Chemo pins' or spikes are used for reconstitution of drugs in vials larger than 20ml. In several centres, drug vials are routinely used for more than one patient for reasons of economy. Sometimes this involves storing reconstituted injections for short periods, if they are known to be stable, either in an isolator or in a fridge. Physico-chemical stability information is taken from Stabilis, local lists or from the manufacturers. The production pharmacist is responsible for microbiological stability.

In one centre in the UK, about 50% of cytotoxic doses are prepared in infusions, 40% as bolus doses and 10% in elastomeric devices.

In the UK, RTU injections of cyclophosphamide, epirubicin and gemcitabine can be purchased and this helps pharmacies to make optimal use of their compounding capacity. In Denmark, compounded cyclophosphamide injection is purchased from the UK because of limited capacity in Demark.

One unexpected finding (from Germany) was that the exterior surfaces of infusion bags from some manufacturers were heavily contaminated with micro-organisms and this was difficult to remove effectively. It was suggested that this contamination might decrease during storage.

Most countries (except the UK) prepare cytotoxic injections with the administration sets already attached. This does not require a great deal of extra work in the pharmacy - it takes less than one minute to attach the administration set.

## Reconstitution and transfer devices

Any new reconstitution and transfer device must make the process safer or faster. Critical features of any new device would be the cost, the extent to which it could reduce environmental contamination and the force required to operate it. Evaluation of reconstitution and administration devices cannot be done at the desk – it is important to work with the nurses and technicians who use the products routinely. Training and education of staff about correct use of products and about safety issues is also critical. In addition, it is important to reassess performance regularly – this is routine in microbiology and a similar approach should be adopted to safe handling of cytotoxic drugs.

## Legislative changes

The panel discussed the impact of the Sharps injury Directive (Council Directive 2010/32/EU of 10 May 2010 implementing the Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector concluded by HOSPEEM and EPSU) and the Council of Europe Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (CM/ResAP(2011)1).

The Sharps injury Directive is aimed at eliminating the risk of injury or infection to healthcare workers from medical sharps. The Directive has to be incorporated in local law and implemented by May 2013. It specifies the minimum requirements that Member States need to implement to protect workers. It calls for elimination of "the unnecessary use of sharps by implementing changes in practice and on the basis of the results of the risk assessment, providing medical devices incorporating safety-engineered protection mechanisms". It also prohibits the recapping of needles and emphasises the importance of regular, comprehensive and ongoing training for staff in the correct use of protective devices and safe systems of working.

The prohibition of recapping (or resheathing) of needles was a particular cause of concern for pharmacists in the UK. Needles are currently resheathed during the cytotoxic preparation process and there would be problems if this could not be done. Pharmacists believe that a distinction should be made between 'clean' needles that are not contaminated with blood or body fluids and contaminated needles that have been in contact with blood or body fluids.

Council of Europe Resolution (CM/ResAP(2011)1 sets out recommendations for quality and safety assurance standards for medicinal products prepared in pharmacies for the special needs of patients. It was inspired by a survey of hospital pharmacy preparation in 19 European countries that identified considerable variation in quality assurance and safety standards across Europe. The working group had concluded that legislation in Europe should be harmonised in order to minimise the risks for patients. The CoE resolution has been accepted by all Member States as a starting point for future legislation. It was formally adopted in January 2011 and pharmacists have been encouraged to approach their

national authorities to discuss implementation of the Resolution. It has been suggested that, if such discussions do not take place, it is possible that alternative, less satisfactory, arrangements could eventually be imposed.

Two important points arising from the Resolution are, first, reconstitution of injections is not considered to be magistral preparation and second, although reconstitution should preferably take place in the pharmacy, 'low risk' products could be reconstituted on the ward. It follows that all products and processes should be risk assessed and a suggested risk assessment scheme is provided in the Resolution. The panel was reminded that 'reconstitution' means preparing the product according to the Summary of Product Characteristics (SPC) and that, if there is any deviation from this procedure, than it is considered to be compounding process.

In the UK, The National Patient Safety Agency (NPSA) has devised a risk assessment scheme for injectable medicines that identifies high-, medium- and low-risk products. However, it is not always possible to compound the high-risk products in hospital pharmacies because there is insufficient capacity.

Panel members suggested that additional factors should be built into the risk assessment, such as the training and quality of the staff involved, whether or not a CSTD is used and the intrinsic toxicity of the drug. In addition, some countries have local risk assessment schemes that give a lower risk weighting to products that are used in-house.

It was also noted that, regardless of risk level, some drugs are too unstable to prepare in the pharmacy. A further complication is that, for some drugs, the shelf lives quoted in SPCs differ from country to country. Panel members agreed that pharmacists should challenge the pharmaceutical industry over this because it is not acceptable to have different values in different countries for the same product.

There were differing views on the future of hospital compounding activity. One viewpoint was that the workload for compounding units could increase over the next ten years because economies of scale will be possible. The alternative viewpoint was that the workload could decrease because the availability oral chemotherapy will increase and the industry could provide more RTU or RTA injections.

The panel concluded that practices relating to the preparation of cytotoxic drugs vary across Europe and, to a certain extent, this is influenced by the availability of products in different countries. Two questions of immediate interest are the optimal frequency with which gloves should be changed and the need for changes of practice to avoid recapping of needles. ●

## Roundtable participants

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