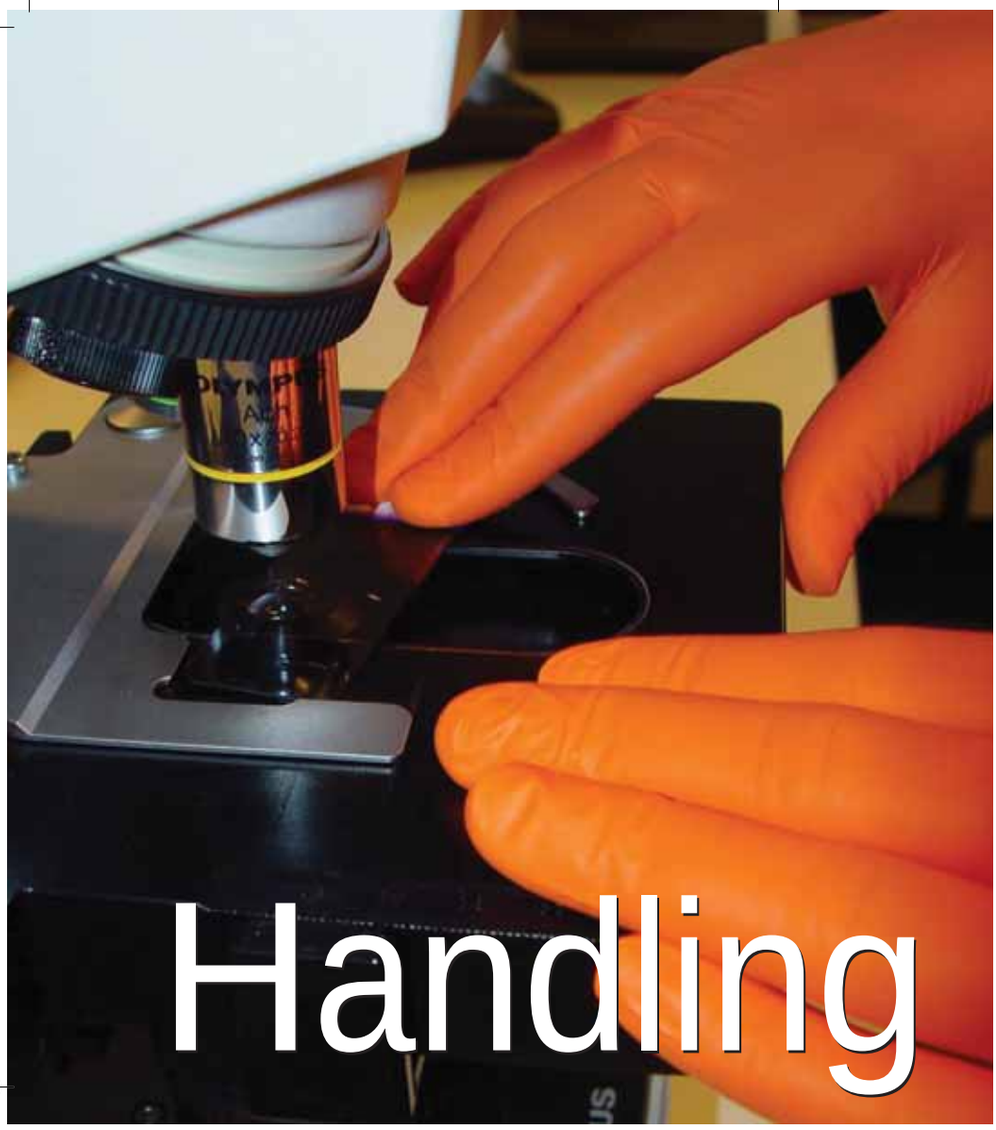

Handling cytotoxic material

The level of protection afforded by gloves to personnel and products when handling cytotoxic agents is complex. **Nick Gardner,** SHIELD Scientific, offers some important considerations

With the 25% increase in cancer in the UK between 1977 and 2006[1] and chemotherapy drugs being at the forefront of our defence for tackling this disease, safety concerns regarding the preparation and handling of cytotoxic agents are likely to increase.

Studies based primarily on animals have led to the International Agency for Research on Cancer (IARC) classifying some cytotoxic drugs as possibly carcinogenic, mutagenic and teratogenic.[2] The potentially hazardous nature of these drugs has caught the attention of the UK Health & Safety Executive (HSE), which has published two information sheets on the subject.[3,4]

Of equal concern is the safety of the product, particularly with reference to microbiological contamination. Today, product protection is tightly controlled by the EC Guide to GMP,[5] which stipulates the precise conditions under which sterile medicinal products are to be manufactured.

The fact that many cytotoxic drugs are hazardous means that, under Control of Substances Hazardous to Health (COSHH) regulations, employers in the UK are obliged to assess the risks.[3] Additionally, concerns regarding the possible carcinogenicity of some anticancer drugs means they are subject to Appendix 1 of the COSHH Approved Code of Practice (ACOP).[3] For operators engaged in the preparation and handling of chemotherapy drugs, the most common form of exposure is via dermal contact and inhalation.[3] Even intact skin is vulnerable[4] and some chemotherapy drugs are skin irritants.[3]

As part of the overall risk assessment, consideration needs to be given to:

- the toxicity of the cytotoxic drug
- the time of exposure to the drug
- the frequency of the exposure to the drug.

As the gloved hand is a likely point of contact during the preparation and administration of drugs, paying particular attention to the glove specification and how it relates to personal protection seems prudent, particularly as the cumulative effect of regular exposure to small doses of cytotoxic drugs[3] is not fully understood.

As most production of anticancer compounds is carried out in enclosed units such as isolators, potential exposure would appear to be limited to the barrier effectiveness of the gloving system. Away from the production unit, skin contact could result from surface residues on packaging or on the vials themselves.

Under the Personal Protection Equipment (PPE) at Work Regulations (1992), appropriate PPE needs to be provided when there are no other alternatives to managing the risks.[3] PPE obviously includes hand protection, which gives rise to the question of how to determine the suitability of the gloves. Where the intended purpose is personal protection, it would seem logical to select a glove registered according to the PPE Directive (89/686/EEC) rather than the Medical Device Directive 93/42/EEC where the emphasis is on patient protection.[6]

Similarly, given the known exposure to chemical hazards, selecting gloves designed to protect against the highest level of risk will be necessary. These gloves are referred to as gloves of complex design (category III) for irreversible or potentially mortal risk.[6] Determining the regulatory status of a glove is simply a question of asking the manufacturer for its Declaration of Conformity (the latter is a legal obligation under the PPE Directive) and the details will often feature on the product data sheet.

The gloves' ability to resist permeation and penetration of cytotoxics is important[4] and requires the following considerations:

Permeation – defined as "the process by

Table 1: Key differences between standards

Comparison	ASTM F 739-99a	ASTM D6978-05	EN374-3:2003
Test Temperature	21ºC (+/-5ºC)	35ºC (+/-2ºC)	23ºC (+/-1ºC)
Permeation rate	0.1µg/cm^2/Min	0.01µg/cm^2/Min Test method as per F 739	1.0µg/cm^2/Min
Scope	Resistance against chemicals in general	Resistance against cytotoxic drugs	Resistance against chemicals in general
Test time	240 minutes	240 minutes	480 minutes
What to test?	No information given on chemicals that need to be tested. Therefore choice and concentration left to the manufacturer	Nine cytotoxic drugs – seven are defined and two additional chemicals to be selected by test house	12 standard chemicals detailed in EN374-1:2003, with no mention of cytotoxic drugs. Thus no specific guidance is given on the selection of cytotoxic drugs
Area of glove needs to be tested	Materials of different thickness to be tested. Outer surface to be in contact with chemical	Palm or cuff, whichever is the thinnest part of the glove & outer side of glove (i.e. that which is in contact with chemical)	Palm area for gloves of homogenous design. Outer surface to be in contact with chemical

Table 2: Comparison of carmustine and thiotepa

Test Chemical	TEST 1: EN 374-3:2003	TEST 2: ASTM D6978-05
Carmustine 3.3mg/ml	No breakthrough was detected up to 240min	Breakthrough in 2.1min
Thiotepa 10.0mg/ml	No breakthrough was detected up to 240min	Breakthrough in 75.5min

Table 3: Annex A (EN374-2: 2003) Quality Assurance Procedure to be used in glove manufacture[9]

Performance level	Acceptable quality level (AQL) unit	Inspection levels
Level 3	<0.65	G1
Level 2	<1.5	G1
Level 1	<4.0	S4

which a chemical agent migrates through the protective glove at a molecular level".[7] Those engaged in a risk assessment, and thus assessing the permeation characteristics of a glove, will inevitably seek data specific to cytotoxic drugs.[8] However, assessors may find glove manufacturers now provide chemical permeation data based on three different standards:

- ASTM D6978-05 "Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs"
- ASMT F739-99a "Standard Test Method for Resistance of Protective Clothing Materials to Permeation by Liquids, Gases Under Conditions of Continuous Contact"
- EN374-3:2003 "Protective gloves against chemicals and micro-organisms – Part 3: Determination of resistance to permeation by chemicals"

While all three norms provide methodologies for chemical permeation, in Europe EN374-3 is often cited as the preferred method, presumably because it is a European standard.[8] However, only ASTM D6978-05 has been specifically developed for testing of gloves for permeation by cytotoxics. Table 1 gives some differences between standards.

Increasingly, ASTM D6978-05 is specified by those engaged in risk assessments, perhaps because this methodology is more aligned with the needs of those preparing or administering cytostatics. In this respect, the test temperature of 35ºC (+/-2ºC) is close to that of the human hand, and it should be noted that permeation accelerates with increasing temperature. In view of the hazardousness of some chemotherapy treatments, it is reassuring that this standard offers the highest level of sensitivity as defined by permeation rate – 100 times more sensitive than the European norm.

In addition, this standard specifically stipulates the cytotoxic agents and their concentrations. Seven are mandatory (carmustine, cyclophosphamide, doxorubicin HCl, etopside, fluorouacil, paclitaxel and thiotepa), while two can be selected by the user. For guidance a selection of 17 chemotherapy drugs and their concentrations are detailed for optional testing.

Finally ASTM D6978-05 explicitly mentions that only the thinnest part of the glove likely to be exposed to chemical contact (i.e. the palm or cuff) is to be tested.

The difference between ASTM D6978-05 and EN374-3:2003 in terms of determining permeation rates is evident from the comparison of carmustine and thiotepa in Table 2. If a risk assessment had been based on EN374-3: 2003, then it could have given the glove wearers a higher level of confidence in the glove's resistance to permeation by carmustine and thiotepa.

As glove thickness and material type are not the only factors that govern permeation; it is suggested that when evaluating permeation characteristics of a glove, only data for a specific glove formulation is considered – this can apply when looking at various formulations of gloves from the same manufacturer or when comparing similar gloves from different manufacturers.[8]

A further cautionary note on assessing the permeation is that the practice of disinfecting gloves in use will diminish their chemical resistance. In contrast to the guidelines in EC Guide to GMP, some authorities recommend not disinfecting gloves when preparing cytostatics.[8]

Penetration – this is described by the HSE as "the bulk flow of a chemical agent through closures, porous material, seams, pinholes and other imperfection in the protective glove".[7] The issue of penetration has been highlighted as a particular concern for operators working in isolators[4] and is especially relevant for isolators under positive pressure, as there is greater potential for leakage of the drug through holes.

As the gloves being used for protection against cytostatics are likely to be registered as Complex Design according to the PPE Directive (89/686/EEC), part of the registration process would have entailed testing them against EN374-2: 2003.[9] For disposable gloves this will invariably mean that the gloves will have undergone a ▶

watertight test and the porosity of a glove is defined by various performance levels outlined in Table 3.

According to EN374-1:2003[10] a glove is considered to be micro-organism resistant if it achieves a minimal Acceptable Quality Level (AQL) of 1.5 or Level 2. An AQL of 1.5 accepts the statistical probability that there are less than 1.5% defects in a batch of gloves. An AQL of 0.65 assumes a tighter quality assurance level, giving the glove wearer a reduced risk of porosity and therefore a higher level of personal protection.

Given that it is recognised that harmful substances can pass through gloves by penetration,[8] sourcing gloves with as low an AQL as possible may be appropriate.

Other considerations for ensuring personal safety are local safety standards. Apart from the HSE, there are other organisations in Europe that have issued specific guidance on the handling and preparation of cytotoxic drugs. They include:

- Berufsgenossenschaft für Gesundheit und Wohlfahrt (BGW) – the professional association for the German health service and social services has produced leaflet M620 "Safe handling of cytostatics"
- TRGS 525 Technical rules for working with dangerous material
- Suva (Schweizerische Unfallversicherungs-anstalt): Check list PPE From. 6709/1
- Institute for Applied Healthcare Sciences (IFAHS) – Quality Standard for the Pharmacy Oncology Service in Germany
- Institut National de Recherche et de Sécurité (INRS) Les médicaments cytstatiques en milieu de soins.
- Toxicité et risques professionnels. Fiche Médico-Technique 33.
- Recommendations pour la prévention des risques professionnels. Fiche Médico-Technique 36

Here too there are differences in guidance (see footnote). For example, glove wearing time is an area where there seems to be some variation in practice. It is notable that the BGW mentions "occlusion" as a reason for changing gloves every 30min.[11] This is because the combination of perspiration and heat generated by occlusion may make it easier for the cytotoxic drugs to come into contact with the skin. Double-gloving for additional protection through a double wall system is widely practised.[8] However, the BGW recommends use of different coloured gloves to help rapid detection of imperfections in the outer gloves.[11]

So far, we have looked at hand protection in enclosed units, where sterile gloves of longer length (28–30cm) are likely to be used. Away from the production unit, exposure could result from surface residues on the packaging or on the vials.

Accordingly, the risk of exposure to hazardous cytotoxic agents may exist and non-sterile protective gloves will need to be worn.

Most of the criteria already discussed still apply, but noting that non-sterile gloves are often thinner and may not have been tested specifically on cytotoxic drugs.[8] The most commonly encountered non-sterile gloves are shorter in length (24cm) and may not protect the wrist fully from drug exposure. The BGW recommends 28cm gloves for contact with cytotoxic agents.[11]

Other considerations are the material properties[8] and compatibility with the rigours of being left on an isolator ring. Not all synthetic gloves may be as suitable as latex, with its superior elasticity. Size range (particularly with reference to smaller and larger sizes) and fit will need to be evaluated. The importance of safety in use should not be overlooked.[8] Grip can be crucial for preventing spillages – a glove in contact with isopropyl alcohol can become very slippery.

Product protection

Annex 1 to the EC Guide to GMP stipulates that "the manufacture of sterile products is subject to special requirements to minimise risks of microbiological contamination, and of particulate and pyrogen contamination".[5] To achieve these objectives, different levels of airborne particles are prescribed for various levels of cleanliness. However, what about the gloved hand, which may be in direct contact with the product? Some authorities refer to the use of "clean gloves" for use in the isolator,[4] without indicating what is clean.

While the glove may be terminally sterilised by gamma irradiation to Sterility Assurance Level (SAL) of 10^{-6} (in accordance with guidelines detailed in ANSI/AAMI/EN ISO 11137:2006 "Sterilization of Healthcare Products – Radiation"), it could still be a source of transmission for particle and pyrogen contamination. Accordingly, it seems prudent to use gloves that have been specifically developed for cleanroom use. The product data sheets for these types of gloves will often provide details in terms of specification and typical levels of particles according to IEST-RP-C005.3.[12] Likewise there may be a claim for low endotoxin content of less than 20 EU/pair of gloves as defined by EN455-3:2000.[13]

Further guarantees of the suitability of the glove for cleanroom use may come from batch specific data that is provided in the form of a certificate of analysis or certificate of conformance. Specifically, with reference to barrier defects such as pinholes, AQL is an important parameter for minimising the risk of product contamination. Given that AQL represents a statistical probability of defects, a lower AQL is better for assuring process protection particularly when working under negative pressure.

The value of cleanliness – particle and extractable data are not routinely provided for surgical gloves, but are for cleanroom gloves. High particle counts on gloves may contribute to increases in bioburden. In addition, cleanroom gloves are typically packaged in paper-free packaging to reduce risk of particle contamination.

The risks associated with endotoxin contamination are particularly relevant to aseptic processes and it has been reported that "the pyrogens that pose most risk to the manufacture of parenteral products are endotoxins".[14] The risks of endotoxin contamination are particularly high as gloves are manufactured in an aqueous environment, which promotes the proliferation of Gram-negative bacteria. Also water used for washing the gloves may be laden with micro-organisms, while raw latex and powder slurries may provide them with a food source. Accordingly, a glove with a low endotoxin content claim and particularly if it is batch tested for endotoxin is likely to be of value to protecting the product.

In terms of protecting hands, endotoxins are inflammatory substances not eliminated by sterilisation and are associated with irritant contact dermatitis and have been reported to accelerate the rate of sensitisation to allergens.[15]

In conclusion, gloves play a vital role in providing personal and product protection and the above-mentioned principles need consideration. CT

Footnote

For a fuller version of this article with the references and additional tables visit the Cleanroom Technology website at www.cleanroom-technology.co.uk

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