

HANDLING OF CYTOTOXIC DRUGS

Am I using the right gloves for protecting myself and the product?

With the 25% increase in cancer in Great Britain between 1977 and 2006¹ 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 classifying some cytotoxic drugs as possibly carcinogenic, mutagenic and teratogenic².

The potentially hazardous nature of these drugs has caught the attention of the HSE, who have published two information sheets on this subject: Safe handling of cytotoxic drugs³ and Handling cytotoxic drugs in isolators in NHS pharmacies⁴ (the latter in association with the MHRA).

Of equal concern is the safety of the product and particularly with reference to microbiological contamination. Nowadays protection of the product is tightly controlled by the EC Guide to GMP⁵, which stipulates the precise conditions under which sterile medicinal products need to be manufactured.

With this in mind, the purpose of this article is to understand how gloves play a vital role in personal safety and protecting the product when handling cytotoxic agents.

Personal protection

The fact that many cytotoxic drugs are hazardous means that under COSHH, employers are obliged to assess the risks⁶. Additionally, concerns regarding the possible carcinogenicity of some anti-cancer drugs means that they are subject to Appendix 1 of the COSHH Approved Code of Practice (ACOP)⁶.

For operators engaged in the preparation and handling of chemotherapy drugs, the most common form of exposure is through dermal contact and inhalation³. Even intact skin is potentially vulnerable⁴ and it is noteworthy that some chemotherapy drugs are skin irritants³.

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

- 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 possibly the most 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.

This may be relevant as the cumulative effect of regular exposure to small doses of cytotoxic drugs³ is not fully understood.

As most production of anticancer compounds is done in an enclosed unit such as an isolator, 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 the packaging or on the vials themselves.

Under the Personal Protection Equipment at Work Regulations (1992), appropriate personal protective equipment (PPE) needs to be provided, when there are no other alternatives to managing the risks³.

PPE obviously includes hand protection, and then the question is how to determine the suitability of the gloves. Where the principle intended purpose is personal protection, it would seem logical to select a glove that is registered >



Comparison	ASTM F 739-99a	ASTM D6978-05	EN374-3:2003
Test temperature	21 °C (+/- 5 °C)	35 °C (+/- 2 °C)	23 °C (+/- 1 °C)
Permeation rate	0,1 µg/cm ² /Min	0,01 µg/cm ² /Min Test method as per F 739	1,0 µg/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 manufacturer	9 cytotoxic drugs - 7 are defined and 2 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 that 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 and outer side of glove (e.g. that which is in contact with chemical)	Palm area for gloves of homogenous design. Outer surface to be in contact with chemical

A comparison table detailing the key differences between ASTM F 739-99a, ASTM D6978-05 and EN374-3:2003

according to the PPE Directive (89/686/EEC) rather than the Medical Device Directive (MDD) 93/42/EEC, where the emphasis is on patient protection⁶.

Likewise, given the known exposure to chemical hazards, selecting only gloves that are designed to protect against the highest level of risk will be necessary. These gloves are referred to as gloves of complex design for irreversible or mortal risk and are often called category III gloves⁶.

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Determining the regulatory status of a glove is simply a question of asking the manufacturer for their 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 cytotoxic drugs is clearly important⁴.

Permeation

Permeation is defined as ‘the process by which a chemical agent migrates through the protective glove at a molecular level’⁷.

For the purposes of assessing the permeation characteristics of a glove, those engaged in the risk assessment will inevitably seek data specifically on cytotoxic drugs. While the shortage of such information was recently reported as a cause of concern⁸, the situation now has improved. Indeed, the complexity has grown to the extent that glove manufacturers

provide chemical permeation data often 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 standard⁸. However, it will be noted that only ASTM D D6978-05 has been specifically developed for testing of gloves to permeation by cytotoxic agents. A comparison table detailing the key differences between these three standards is provided above.

Focus on ASTM D D6978-05

Increasingly ASTM D6978-5 is being specified by those engaged in risk assessments. This may be because this methodology is more aligned with the needs of those preparing or administering cytostatics.

In this respect the test temperature of 35° C (+/- 2° C) is close to that of the human hand, while it should be noted that with increasing temperature permeation accelerates.

In view of the hazardousness of some chemotherapy treatments, it is reassuring to note that this standard offers the highest level of sensitivity as defined by permeation rate - in fact, 100 times more sensitive than the European norm.

In addition, only this standard specifically stipulates the cytotoxic agents and their concentrations. Seven are ▷

mandatory (Carmustine, Cyclophosphamide, Doxorubicin HCl, Etoposide, Fluorouracil, 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 which is likely to be exposed to chemical contact (e.g. 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 following comparison on Carmustine and Thiotepa:

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

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 to Carmustine and Thiotepa.

As glove thickness and material type are not the only factors that govern permeation, it is suggested that when evaluating the permeation characteristics of a glove only the data for a specific formulation is considered.

This could apply to various formulations of gloves from the same manufacturer and when comparing similar gloves from different manufacturers⁹.

A further cautionary note on assessing the permeation properties of gloves is that the practice of disinfecting gloves in use will inevitably diminish their chemical resistance properties. In contrast to the guidelines in EC Guide to GMP⁵, some authorities recommend not disinfecting gloves when preparing cytostatics.⁸

Penetration

Penetration 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 isolators⁴. This is especially relevant for those isolators working under positive pressure, as there is potential for leakage of the drug through holes⁴.

As the gloves that are being used for personal 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: 2003⁹.

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.

According to EN374-1:2003¹⁰ 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. ▶



Annex A (EN374-2: 2003) Quality Assurance Procedure to be used in glove manufacture⁹

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

Given that it is recognised that harmful substances can pass through gloves by penetration⁸, sourcing gloves with as low an AQL as possible may be appropriate.

Other considerations for ensuring personal safety

Local Safety Standards (some of them are mentioned below):

Apart from the HSE, there are a number of other organisations in Europe that have issued specific guidance on personal safety for the handling and preparation of cytotoxic drugs.

These include the following:

- Berufsgenossenschaft fuer Gesundheit und Wohlfahrt (BGW) - the professional association for the German health service and social services has produced a leaflet M620 'Safe handling of cytostatics', which is frequently cited in the literature
- TRGS 525 - technical rules for working with dangerous material
- Suva (Schweizerische Unfallversicherungsanstalt) - check list PPE Form. 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 cytostatiques en milieu de soins; toxicité et risques professionnels. Fiche Médico-Technique 33; recommandations pour la prévention des risques professionnels. Fiche Médico-Technique 36

The table below provides some insight to the guidance issued by the HSE, Berufsgenossenschaft fuer Gesundheit und Wohlfahrt or BGW (Germany) and the Institute for Applied Healthcare Sciences or IFAHS (Germany).

Glove wearing time is an area where there seems to be some variation in practice. In this respect it is noteworthy that the BGW mentions occlusion as a reason for changing gloves

every 30 minutes¹¹. This is because the combination of perspiration and heat which is generated by occlusion may make it easier for the cytotoxic drugs to come into contact with the skin.

Double-gloving in order to enjoy the additional protection afforded by a double wall system is widely practiced⁸. However, the BGW recommends the use of coloured gloves in order to detect more quickly imperfections on the surface of the outer gloves¹¹.

So far we have largely been looking at the question of hand protection in the area where chemotherapy drugs are reconstituted. This is typically done in an enclosed unit, where sterile gloves of longer length (28cm to 30cm) are likely to be used.

Away from the production unit, exposure could result from surface residues on the packaging or on the vials themselves. Accordingly, the risk of exposure to hazardous cytotoxic agents may exist and non-sterile protective gloves will need to be worn.

Again, much of the criteria that has been discussed for gloves in the production unit still applies, but noting that non-sterile gloves are often thinner and may not have been tested specifically on cytotoxic drugs⁸.

The most commonly encountered non-sterile gloves are shorter in length (24cm) and these may not be suitable if protection of the wrist from exposure to drugs is sought.

Interestingly, the BGW specifically recommends gloves with a length of 28cm for contact with cytotoxic agents¹¹.

The discussion up until now has tended to focus on the permeation and penetration properties of gloves. Other considerations may be material properties⁸ and their compatibility with the rigours of being left on an isolator ring.

In this respect not all synthetic gloves may be as suitable as latex due to the superior elasticity of latex. Size range - particularly with reference to the smaller and larger sizes - and fit will need to be evaluated.

Comparison of the features and benefits of different guidance	BGW ¹¹	IFAHS ⁸	HSE ^{3&4}
Gloving system and thickness	Minimum of 0.3mm thickness. Double-glove with two different colours	Double-gloving recommended	No specific guidance
Minimum length	Minimum 28 cm	No specific guidance	No specific guidance
Glove wearing time	Change after every 30 minutes, regardless of visible contamination or damage	Change after shift - up to 3 hours or 180 min and/or when contaminated	Change gloves at least every 4 hours when working in isolator
AQL - resistance against penetration/freedom from holes	Mentions AQL 1.5 as per EN 455-1 for medical gloves	Mentions AQL 1.5 as per EN 455-1 for medical gloves or AQL 0,65 or 1,5 or 4 as per EN 374-2	No specific guidance
Recommended norm for permeation testing of cytotoxic agents	EN 374-3	EN 374-3	No specific guidance
Avoidance of allergies	Powder-free gloves. If latex use only those with low latex protein content. Synthetic latex preferred	Use powder-free latex gloves. Select latex gloves with low latex protein content (<30µg/g if possible). Use thiuram free to reduce risk of allergic contact dermatitis	If latex gloves are used then a risk assessment as part of COSHH needs to be undertaken
Other glove-related requirements	Use good fitting gloves	Vinyl gloves are not recommended due to low chemical resistance and poor fit	In isolators operating under negative pressure, it is essential that only well-fitting gloves are used to avoid ballooning

The importance of safety in use should not be overlooked⁸. Grip can be crucial for minimising spillages and yet a glove in contact with isopropyl alcohol can become very slippery.

Product protection

Annex 1 to the EC Guide to GMP mentions that “the manufacture of sterile products is subject to special requirements in order 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 isolator⁹, 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-C005.3¹². Likewise there may be a claim for low endotoxin content of less than 20 EU/pair of gloves as defined by EN455-3:2000¹³.

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.

Conclusion

Gloves play a vital role in terms of providing personal and product protection. Mention was made of the different regulatory status of gloves and it would appear that those that are registered as Complex Design (Category III) according to the Personal Protective Equipment Directive (89/686/EEC) are the most appropriate.

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In view of the potentially hazardous nature of some cytotoxic drugs, determining the glove’s ability to withstand exposure is important. For permeation assessing a glove on the basis of a test methodology which is significantly more sensitive and has been specifically developed for chemotherapy drugs could be beneficial (ASTM D6978-05).

In terms of penetration, selecting gloves with as low an AQL (Acceptable Quality Level) for barrier defects as possible may enhance the level of personal and process protection.

Given the emphasis on product protection, consideration needs to be given to the compatibility of the gloves with the environments where cytotoxic drugs are handled and prepared. In this respect a glove specifically developed for cleanroom use may bring the benefit of reducing the risk of microbiological contamination.

Recommendations

- For personal protection against exposure to cytotoxic drugs, use only gloves that are registered as Complex Design (Category III) according to Personal Protective Equipment Directive (89/686/EEC)
- Use longer length gloves (>28cm) in order to allow glove wearer to roll cuff over the garment sleeve, thereby providing adequate wrist protection
- In order to determine the permeation of a glove to cytotoxic agents request data based on ASTM D6978-05
- Selecting gloves with an AQL of <0.65 for pinholes may provide greater product and personal protection
- Only Cleanroom gloves should be used because they offer a higher level of cleanliness and are packed in paperless packaging
- To minimise the risk of microbiological contamination, select gloves that are batch tested for particles and endotoxin. These details are furnished on the certificate of analysis or conformance

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