

# Understanding closed system transfer devices

Containment of hazardous drug vapour by closed system transfer devices is critical; new test methods are providing valuable insights into the performance of these devices and recent studies are suggesting new potential applications

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The use of closed system transfer devices (CSTDs) should be obligatory whenever cytotoxic or other hazardous drugs are prepared, administered or disposed of, according to Paul Sessink (Managing Director, Exposure Control, Sweden). This is because occupational exposure to cytotoxic drugs poses recognised risks of mutagenicity, carcinogenicity and reproductive toxicity. However, engineering controls, such as biological safety cabinets, do not always provide adequate protection for workers. Studies with CSTDs show substantial reductions of environmental contamination with cytotoxic drugs when the devices are used – and this should reduce potential adverse health effects. A further point to note is that CSTDs are containment devices and the use of such devices has a higher priority in the hierarchy of protection measures than engineering controls, administrative controls and personal protective equipment.

Dr Sessink drew attention to a recent publication of the European Biosafety Network, which calls for a common (European) definition of CSTDs, including the technical specifications to be met by a medication transfer system to be considered as a closed system, and harmonised protocols for testing CSTDs.<sup>1</sup>

### Challenges in selecting a CSTD

Selecting a suitable CSTD is not always a straightforward process, explained Jay Brown (Director of Pharmacy Oncology, Specialty and Infusion Services, Novant Health Oncology Specialists, Winston-Salem, North Carolina, US). An ASHP



Dr Paul Sessink

survey published in 2012 showed that only 21% of health institutions had previously used CSTDs.<sup>2</sup> The available CSTDs are based on several different mechanisms to achieve ‘closedness’ and may not be directly comparable. For example, some rely on a physical barrier or expansion balloon to contain drug vapours or aerosols and others use filtration or air cleaning systems. In addition, different methods of assessment have been used to support claims of being ‘closed systems’. The decision about which CSTD to use may also be driven by outside influences such as the nursing leaders’ views and costs to the institution, he added.

United States Pharmacopeia (USP) General Chapter 800 provides standards for safe handling of hazardous drugs to minimise the risk of exposure to healthcare personnel, patients and the

environment. It recommends evaluation of existing CSTDs based on published, peer-reviewed data and containment studies. It also requires the use of a CSTD in hazardous drug administration, emphasised Dr Brown. However, it does not require the use of CSTD in compounding of hazardous drugs and it does not guarantee 100% hazardous drug containment through the use of CSTDs.

In 2014 the Food and Drug Administration (FDA) created a product code specifically for CSTDs (the FDA ONB code). This defines as CSTD as:

- “a product that reconstitutes and transfers antineoplastic and other hazardous drugs in the healthcare setting, and
- is indicated to reduce the exposure of healthcare personnel to chemotherapy agents in healthcare settings”.<sup>3</sup>



Dr Jay Brown

The National Institute for Occupational Safety and Health (NIOSH) (in the US) defines as CSTD 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.”<sup>4</sup> This is a performance standard rather than a technical specification, noted Dr Brown.

#### Evaluation of CSTDs

Testing the efficacy of a CSTD depends on the type of CSTD and its intended purpose – whether it is for use in injection preparation, administration or for waste disposal of cytotoxic drugs. One thing that is very important is that real drugs should be used in the testing process and not surrogate agents that could behave differently, said Dr Sessink. Another danger is that surrogates might damage the integrity of the CSTD and lead to false positive results, he warned. Testing should be undertaken initially under laboratory conditions but devices should also be evaluated in the ‘in use’ situation to reflect normal practice.

One way of assessing the performance of a CSTD is by measuring the amount of drug that is released into the environment. In practice this can involve wipe-sampling of surfaces, air sampling to check for release of particles and analysis of absorbent mats (if used). Sampling of gloves is important because they can be a route for skin contamination and absorption. Finally, urine analysis provides definite evidence of exposure, although not the route of exposure, said Dr Sessink.

#### Pitfalls of testing

“No CSTD system is 100% closed and much depends on the test process”, Alan Wilkinson (Managing Director, Biopharma Stability Testing Laboratory (BSTL) Ltd, Nottingham UK) told the audience. The challenge agent used in the test procedure should be chemically inert and in other respects behave in a “drug-like” way, he continued. Highly reactive chemicals, such as titanium tetrachloride are therefore not suitable. Isopropyl alcohol (IPA) was originally proposed by NIOSH as a challenge agent. It is inert but has a very high vapour pressure, unlike most injectable drugs. When used in vapour-containment tests, it can be shown that all CSTDs leak IPA, if a suitably sensitive detector is used. Fluorescent dye (fluorescein) has previously been suggested as a way to assess leakage of liquid droplets but Dr Wilkinson questioned the scientific validity of the test methodology. In practice, it is almost impossible to distinguish between light emission from liquid on the surface of the container and liquid inside the CSTD-drug vial assembly. Other factors, such as the intensity and bandwidth of the light excitation source, can dramatically alter the results obtained.

#### NIOSH protocol

In 2015, NIOSH published a draft protocol for testing the vapour containment performance of physical barrier CSTDs (but not for the air cleaning/filtration type) in which the challenge agent was 70% IPA, Ian Pengelly (Principal Chemist, Analytical

Chemistry Team at the Health and Safety Laboratory of the United Kingdom Health and Safety Executive) explained. The idea behind it was that pharmacists would build their own apparatus and carry out testing – a scenario that Dr Pengelly described as being “unlikely”. After consultation a new draft universal test protocol was published in 2016. This included nine potential surrogate compounds for use as challenge agents and used thermal desorption followed by gas chromatography and mass spectrometry (TD-GC-MS) for detection. This is a method that is capable of detecting parts per billion, in contrast to the infra-red detection method in the original protocol that can only detect parts per million. The new procedure is designed for use in accredited testing laboratories rather than pharmacies, noted Dr Pengelly.

The principle of the new, universal protocol is that manipulation of, for example, a cytotoxic drug, is carried out in a sealed chamber so that leakages can be detected. Two air sampling devices containing a sorbent (Tenax) are positioned inside the chamber and used to collect air samples. Results are generated by a process of thermal desorption followed by gas chromatographic separation and mass spectrometry (TD-GC-MS).

So far, more than 250 separate tests on three different CSTDs, using 2.5% solution of 2-phenoxyethanol (2-POE) as the challenge agent (following the universal protocol), have been carried out at an independent laboratory in the UK (BSTL). The popular perception is that physical barrier type CSTDs are superior to air cleaning/filtration types but the results show that both Tevadaptor (filtration type) and BD-PhaSeal (barrier type) release less than 0.71ppb (the limit of quantitation). In contrast, the Chemoclave released 2.7–7.3 ppb and the needle and syringe (open) method released more than 4.00 ppb. This difference can be attributed to the use of double-membrane connectors between vial and syringe adaptors rather than Luer locks, said Dr Wilkinson. “The data presented clearly show the Luer lock connection provides a health worker with less protection than the open system using a needle and syringe”, he added.

NIOSH has proposed nine potential surrogate compounds, including 2-POE, for use as challenge agents. Isopropyl



Dr Alan Wilkinson

alcohol has a vapour pressure of 4400 Pascals (Pa) whereas commonly-used cytotoxic drugs, including cyclophosphamide and fluorouracil have vapour pressures of less than 0.01 Pa.

“IPA is a solvent and does not behave like any hazardous drug”, said Dr Wilkinson.

He concluded that 2-POE is a safe and suitable challenge agent for testing the containment performance of all CSTDs,

regardless of what technology they employ.

#### **Tevadaptor performance**

The next step was to test the ability of a CSTD to contain hazardous drug vapour, rather than a surrogate substance. Dr Wilkinson described a study that had been carried out in his laboratory in the UK.

A CSTD (OnGuard/Tevadaptor) was used to reconstitute a vial of cyclophosphamide, as it would be when in routine use. The cyclophosphamide vial was placed in a water bath at 50°C inside a sealed glass chamber. This increases the vapour pressure of the drug above the normal (room temperature) value and provides a “really serious challenge to the OnGuard (Tevadaptor) technology and specifically the ToxiGuard vapour capture system”, said Dr Wilkinson. Nitrogen was fed into the vial at a rate of 300ml/min, via a 21-gauge needle inserted through the adaptor. The tip of the cannula was above the surface of the drug solution.



The BSTL environmental test chamber as used to replicate the NIOSH test protocol for assessment of CSTD systems.

“This experimental design follows a method described in a published protocol”, commented Dr Wilkinson. The effect of the nitrogen flow is to present constantly saturated cyclophosphamide vapour to the ToxiGuard filtration system of the Tevadaptor CSTD. If the CSTD system remains effective then nitrogen gas will flow through the 0.2 micron filter and the ToxiGuard activated carbon membrane, providing pressure equalisation at all times, but the drug will be retained. The exit tube from the apparatus (carrying the exhaust nitrogen) goes to a cold trap (at -90°C) so that all of the vapour that is released by the system is captured. In addition, the rinsate from the trap plus washings from the internal surfaces of the apparatus was analysed using liquid chromatography with tandem mass spectrometry (LC-MS/MS) equipment capable of detecting as little as 10 picograms of cyclophosphamide.

The activated charcoal membrane was being challenged with cyclophosphamide vapour – one of the most volatile hazardous drugs in existence – at 50°C at a flow rate of 300ml/minute for 24 hours, and even under these stringent test conditions, the results consistently showed that the amounts of cyclophosphamide that escaped was below the limit of quantitation, suggesting that the ToxiGuard filter was capturing all of the drug, said Dr Wilkinson. The ToxiGuard filters were later removed and extracted to determine the amounts of cyclophosphamide trapped. The results showed that in two (out of five replicates) the amount of cyclophosphamide detected exceeded 10,000 nanograms.

“This study provided two robust pieces of evidence – first, there was no cyclophosphamide outside the Tevadaptor CSTD/drug vial assembly and, second, the ToxiGuard filter captured and retained 100% of the cyclophosphamide vapour. A flow rate of 300 ml/hour for 24 hours means that the CSTD was challenged with 432 litres of cyclophosphamide-containing vapour, whereas in normal use a volume of 100ml might be pushed through a CSTD – so we conclude that OnGuard/Tevadaptor is 100% effective”, said Dr Wilkinson.

#### Exposure to antibiotics

Occupational exposure to antibiotics can be a serious hazard, according to Dr Sessink, with effects ranging from hypersensitivity and allergies to



Dr Ian Pengelly

anaphylactic shock. In addition, health care staff can harbour resistant organisms as a result of frequent exposure. Nurses have reported seeing splashes and leakages during preparation of injections and experiencing a bitter taste. The Swedish Work Environment Authority has recently established a maximum limit for penicillin of 0.1mg/m<sup>3</sup> as inhalable dust.

Pilot studies in Sweden and Hungary assessed the effectiveness of the Tevadaptor CSTD to reduce environmental contamination with antibiotics (vancomycin, Augmentin, ceftriaxone and meropenem in Hungary, and cefotaxime, piperacillin, benzylpenicillin, vancomycin, ceftriaxone and meropenem in Sweden). Baseline studies showed that the needle and syringe method of preparation was associated with widespread contamination. The introduction of the CSTD resulted in substantial, statistically significant reductions in the levels of contamination with all antibiotics in Hungary, and with four out of six in Sweden. There were no reduction in the

levels of ceftriaxone and meropenem in some positions and the reasons for this are not clear, said Dr Sessink.

#### References

- 1 Preventing occupational exposure to cytotoxic drugs. Sessink PJM, Sewell G, Vandenbroucke J (eds). [www.europeanbiosafetynetwork.eu/preventing-occupational-exposure-to-cytotoxic-drugs/](http://www.europeanbiosafetynetwork.eu/preventing-occupational-exposure-to-cytotoxic-drugs/) (accessed April 2017).
- 2 Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: dispensing and administration 2011. *Am J Health Syst Pharm* 2012;69:768–85.
- 3 US Department of Health and Human Services. [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=ONB](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=ONB).
- 4 Nygren O et al. NIOSH Definition of closed-system drug-transfer devices. *Ann Occup Hyg* 2009;53:549.

The satellite symposium, *Containing hazardous drugs with CSTDs: Understand the evidence and requirements from USP 800 to the NIOSH Universal Testing Protocol* was held during the ASHP Midyear Clinical Meeting, Las Vegas USA in December 2016. The symposium was sponsored by B Braun USA, which markets OnGuard / Tevadaptor in the US.

#### Key points

- Closed system transfer devices (CSTDs) should be tested for vapour containment using suitable surrogate agents and with actual hazardous drugs.
- 2-Phenoxyethanol 2.5% is a safe and suitable surrogate agent for vapour-containment testing.
- Both Tevadaptor (filtration-type) and BD-PhaSeal (barrier-type) CSTDs contain vapour effectively when tested using the NIOSH protocol.
- Rigorous testing of the Tevadaptor shows that it is 100% effective at containing cyclophosphamide vapour.