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CSTDs prevent microbial ingress

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A second-generation closed system transfer device both provides effective containment of hazardous drugs and prevents microbial ingress for a prolonged period and could therefore enable more economical use of expensive products

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Over the past 20–30 years studies have established that healthcare personnel can be exposed to hazardous drugs in the course of their work. Such exposure leads to adverse events including biological marker changes, chromosomal damage and reproductive toxicity. Closed system transfer devices (CSTDs) are now recommended for preparing and administering hazardous drugs in order to protect healthcare personnel and others from exposure.1,2

CSTDs should make it possible to reconstitute powders and transfer solutions without leakage of droplets, aerosols or vapours. They should also make it possible to connect and disconnect syringes or bags of cytotoxic drug solutions without leakage of droplets, aerosols or vapours. All this has to be achieved without allowing ingress of particles or microorganisms. In addition, any CSTD also has to be easy to use correctly and robust in use.

Available devices
A number of devices have been developed for this purpose, including BD PhaSeal (BD), ChemoClave (ICU Medical), Texium and SmartSite (Carefusion), OnGuard/Tevadaptor (B Braun/Teva) and Equashield. One important feature is the way in which they deal with the under- and over-pressures that can develop during the reconstitution and aspiration processes. This is critical because it can be a source of aerosol formation. Some devices use an expansion balloon, whereas others use filters to allow air in and out without releasing the drug substance. Here, we focus on the Equashield device, which has been developed to address some of the problems encountered with the first generation of CSTDs.

The Equashield closed system transfer device has a unique mechanism of action. It is a fully self-contained unit comprising a sealed, two-compartment syringe with a dual needle, air-to-liquid closed exchange system. The upper end of the barrel is sealed. The plunger rod is made of metal and cannot be detached from the syringe. The air-to-liquid closed exchange system allows equalisation of pressure differentials during the transfer process. When drug solution is withdrawn from a vial it is drawn through a short needle into the syringe (in the usual way); at the same time air from the air chamber at the upper end of the syringe is transferred to the vial via the long needle.

CSTD studies
Studies of CSTDs can be divided into two categories – those that assess some aspect of device function (for example, ability to prevent leakage of liquid or vapours) and those that assess the outcome of using the device in routine practice (for example, environmental contamination studies).

Efficiency of dry connectors
Dry connectors are an important feature of CSTDs and the corresponding administration sets. The efficiency of dry connectors has been assessed using a number of surrogate markers including radioactive technetium, platinum, fluorescein and acidic solutions. A study using fluoroscein compared the Equashield device with BD PhaSeal and the Tevadaptor/OnGuard system. Leaks were detected in all the Tevadaptor/OnGuard devices, in 40% of the BD PhaSeal devices and in none of the Equashield devices.3

Vapour containment efficiency

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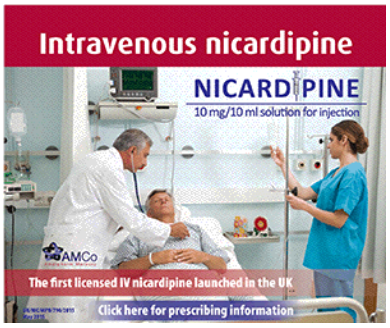

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The potential for vapour leakage from drug transfer devices has been examined using titanium tetrachloride as the drug simulant.4 Titanium tetrachloride generates visible 'smoke' when in contact with moisture in the air. Therefore, if titanium (vapour) leaks from a transfer device, then 'smoke' will be formed outside the device.

A study compared Equashield with three other devices (BD PhaSeal, Chemoprotect (Codan) and Tevadaptor/Onguard) using the method previously described.5 The results showed that the closed systems with full pressure equalisation (that is, Equashield and BD PhaSeal) prevented the release of titanium vapour.

Syringe plunger contamination risk
Cytotoxic drug contamination arising from the syringe plunger has been identified as a factor contributing to contamination of the workplace, in particular contamination of gloves and the work surface in the biological safety cabinet or isolator.6 Multiple studies have been carried out on syringe plunger contamination risks. One such study compared BD syringes attached to BD PhaSeal devices with Equashield devices using cyclophosphamide as the marker drug.7 Significant contamination was detected on 11 out of 12 BD syringes but on none of the Equashield CSTDs.

A recent study evaluating the contamination potential of three syringes (BD, Covidien and Equashield) used for compounding cyclophosphamide demonstrated no detectable contamination with the Equashield device versus contamination in 62.5–100% of the other s.8

eness – prevention of surface contamination
ely the effectiveness of a CSTD is measured by the extent to urface contamination in the working area is reduced when it is study in the USA assessed the impact of implementing ield in an ambulatory cancer chemotherapy infusion centre.9 isly the Chemo Dispensing Pin (B Braun) had been routinely he results showed cyclophosphamide contamination in both the acy and the infusion suite had fallen to non-detectable levels one er the Equashield device had been introduced.

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Prevention of microbial ingress
If a containment device can prevent hazardous drugs from escaping, then it follows that it should be able to prevent the ingress of other substances including micro-organisms. In recent years, there has been growing interest in the possibility of using CSTDs to preserve the microbiological integrity of compounded products. The objective here is to be able to keep the compounded product for long enough to allow its use for subsequent doses. In some cases, where expensive drugs are involved, this could lead to very considerable savings. It might even be argued that the devices pay for themselves in such scenarios.

Challenge studies to investigate the potential for CSTDs to preserve the microbiological integrity of products have been devised. Such studies are designed to simulate the situation that would exist if single-use vials of reconstituted drugs were used for preparation of more than one dose. They involve fitting CSTDs on vials of growth media, artificially contaminating the access membrane surface with a suitable inoculum (usually more than 103 colony forming units) of a suitable microorganism. After allowing the inoculum to dry, the surface is swabbed with disinfectant (usually 70% isopropyl alcohol) and a sample is withdrawn. Several samples are taken and at the end of the test period the vial is incubated to check for microbial growth. All manipulations are performed under ISO 5 conditions to simulate the real-life situation

One challenge study compared the potential of four CSTDs (Chemoprotect spike, Clave connector, PhaSeal and Securmix) to prevent microbial ingress.10 The authors concluded that BD PhaSeal was associated with the lowest level of transfer of micro-organisms and that adequate decontamination of vial tops (by spraying and swabbing) was required before puncture. However, the authors noted that the high levels of microbial contamination used in the study were unlikely to occur in practice.

Subsequent studies11,12 concluded that BD PhaSeal had demonstrated the potential to prevent microbial ingress for a period of seven days.
A 2014 challenge study using the Equashield device applied more stringent conditions (longer study period, more vial punctures, inoculation with bacteria before each puncture) than previous studies.13 In this study, vials of growth media were fitted with Equashield Vial Adaptors on day 1 and then incubated for two days. The seven-day challenge study was started on day 3. During the study the vials were subjected to ten, seven or five inoculation-disinfection-access-transfer cycles over a seven-day period. In total, 770 access-transfer operations were performed during the course of the study. At the end of the study, all vials were incubated again and no growth was seen in any of them.

Economical use of drugs
In 2008, it was suggested that expensive drugs could be used more economically if the unused portions of the vials of reconstituted drugs were to be saved and used for preparation of subsequent doses instead of being discarded.14 The authors calculated that savings could amount to more than €100,000 per annum (at 2008 prices).

Clearly, this is only possible if the drug in question is chemically stable for a suitable length of time and if the microbiological integrity of the reconstituted product can be assured.

It is a requirement of USP 797 that single-use or non-preserved drugs must be discarded six hours after the vial is accessed for the first time so long as the vial is accessed and remains in ISO class 5 environment, otherwise it must be discarded after one hour. In an audit of one of the oncology infusion clinics at Indiana University Health, the annual drug acquisition cost was approximately $15.5 million and it was estimated that more than $1 million residual drug product was discarded due to the USP 797 standard.11

A recent study at The Mount Sinai Hospital, NY, USA, found that implementation of beyond-use date of chemo/biotherapy single-dose vials using Equashield resulted in significant cost savings to the institution of $44,192 during the one-month study period, translating to an estimated cost savings of approximately $530,000 annually.15

The evidence described above suggests that CSTDs could provide a means of ensuring that reconstituted products remain microbiologically stable for long enough to allow the unused portion of the drug solution to be used for subsequent preparations. This process has been described as ‘drug vial optimisation’. It could be of value to health services because it reduces unnecessary wastage of viable pharmaceuticals and therefore could produce significant cost savings for the healthcare system. In addition it would be beneficial for the ment.

ısions

echnology is advancing and second generation CSTDs, such ashield, offer a number of advantages over the earlier products. gh originally conceived to reduce contamination of the workplace zardous drugs, the barrier properties of CSTDs could usefully oited to make more economical use of expensive drugs. ıield has undergone particularly stringent microbiological testing results suggest that it would be suitable for use in preserving robiological integrity of reconstituted products so that they may be used more economically. It is, of course, the responsibility of purchasers and users of CSTDs to satisfy themselves that CSTDs meet the required performance criteria.

Key points

- Closed system transfer devices (CSTDs) must incorporate a reliable mechanism to equalise under- and over-pressures during the preparation process so as to avoid release of aerosols.
- The Equashield CSTD is a self-contained unit comprising a two-compartment syringe with a dual needle, air-to-liquid closed exchange system and a sealed barrel.
- CSTDs (Equashield and BD PhaSeal) could be used to preserve the microbiological integrity of reconstituted drugs so that the unused portion could be used to prepare subsequent doses.
- The Equashield device has undergone more stringent microbiological testing than other CSTDs.
- The exposed syringe plunger can be a source of chemical contamination inside the biological safety cabinet or isolator.

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