The use of an air-cleaning CSTD enables extending the beyond use date (BUD) of a single-use vial to 28 days after first puncture

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Introduction

- There is an increasing pressure on hospital pharmacists to reduce the drug cost burden and to preserve drugs that are of shortage at a time of increasing healthcare costs, especially with respect to biological drugs.[1]
- Extending the practical beyond use date (BUD) of a non-preserved drug vial, through the use of closed system transfer devices (CSTDs), may offer a solution to this problem by drug vial optimization (DVO).
- CSTDs were originally developed to protect personnel working with CMR (Carcinogenic, mutagenic and reprotoxic) agents. However, in addition to personal protection, product protection is also very important to avoid infections of patients.
- Hence, in addition to prohibiting the escape of hazardous drugs or vapor concentrations outside the system, the National Institute of Occupational Safety and Health (NIOSH) also defined the CSTD as a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system.[2]
- Summary of Product Characteristics (SPC) generally assumes that a parenteral drug is prepared in an uncontrolled environment (i.e., in a clinical ward). The assumption is that the drug is prepared by dissolving and/or diluting it immediately before use, administered to the patient, and then discarded.
- In practical use, the limited number of vial sizes, variable/low number of patients seen in the clinic per day, and the often-deferred treatment per patient result in residual drug solutions when compounding personalised doses. This, together with the limited physical and chemical in-use stability data provided in the Summary of Product Characteristics (SPC), results in drug waste and significantly burdens the cost of healthcare.
- In recent years, numerous independent stability studies demonstrated the possibility to significantly extend the shelf-life of parenteral medicines after first use.[3] These studies enable one to use these drugs for longer than specified in the SPC, assuming that the drug is prepared in a controlled, bacteria-free, environment.
- Currently, all CSTDs approved by the FDA are authorized to be used for up to 7 days and 10 activations.
- A previous study demonstrated that an air-cleaning CSTD, the Tevadaptor® (Simplivia), allows one to extend the BUD of a single-use vial up to 28 days, by demonstrating maintenance of microbiological sterility eventhough the drug was prepared in an uncontrolled ("hospital ward") environment.[4]
- A new generation of air-cleaning CSTD, the Chemfort® (Simplivia), was recently approved by the FDA (Sep. 2021). In a previous study, the Chemfort prevented the escape of hazardous drugs up to 28 days and 10 activations.[5]
- The aim of the current study was to examine whether maintenance of microbiological integrity for up to 28 days and 10 activations can be achieved in an uncontrolled environment for this CSTD as well.

Material and Methods

- In this study, 350 vials containing 100 ml of Tryptic Soy Broth (TSB, USP compliant) were used.
- Prior to the study, TSB medium was tested for pH (avg.: 7.3; range: 7.1-7.5), sterility (in 3% or up to 20 samples), and growth capability (using various test organisms as described in Table 1, according to the United States Pharmacopeia, USP).
- Before accessing each vial, the Chemfort® vial adaptor septum was wiped with 70% IPA and allowed to dry.
- All aliquots (5 ml) were withdrawn from each TSB vial to 10 mL syringes (Omnifix® Luer Solo single-use syringes, BBraun®), using Chemfort Vial Adaptor (VA) and Chemfort Syringe Adaptor Lock (SAL) as illustrated in Figure 1.
- On days 1 and 14, 3 aliquots were withdrawn from each vial. On day 28, 4 additional aliquots were withdrawn from each vial. This schedule resulted in a total of 1,050 syringes on day 1, 1,050 syringes on day 14, and 1,400 syringes on day 28 (Figure 2).
- All syringes were incubated for 7 days at 22.5±1°C and for 7 additional days at 32.5±1°C, and then visually inspected for signs of microbial growth (turbidity).
- Following withdrawal of the final samples on day 28, the vial containing the remaining growth medium (50 mL) was incubated for 14 days at 32.5±1°C, and then examined for microbial growth.
- As a positive control, the growth capability of the TSB medium on day 42 was confirmed by inoculating 10 test containers with < 100 colony forming units of various test organisms as described in Table 1, according to the European Pharmacopeia (Ph. Eur).[6]
- 10 unused containers served as negative controls.
- In order to ensure that an uncontrolled environment was maintained throughout the study, active and passive monitoring of air quality was performed.

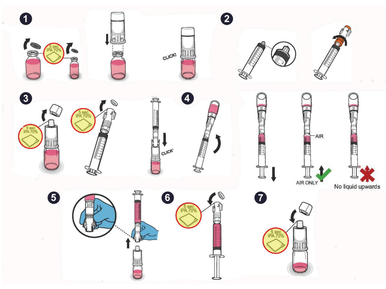

Fig. 1: Handling procedure

The CSTDs were handled as described in the device's instructions for use (IFU).7 Prior to connecting the CSTD, the rubber stopper of the vial containing 100 mL sterile TSB growth medium was disinfected with 70% IPA (Quickpads) with an intense circular motion for 3 to 15 seconds (step 1). Each time a syringe with a connected Chemfort® Syringe Adaptor Lock was attached to the vial adapter of the TSB vial, both the Chemfort® vial adaptor and the Syringe Adaptor Lock septa were wiped with 70% IPA and allowed to dry (steps 3, 6 and 7).

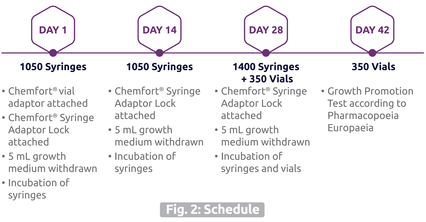

Fig. 2: Schedule

Microorganism	ATCC No
Staphylococcus aureus	6538
Bacillus subtilis	6633
Kocuria rhizophila (M. luteus)*	9341
Clostridium sporogenes**	11437
Escherichia coli	8739
Pseudomonas aeruginosa	9027
Candida albicans	10231
Aspergillus brasiliensis	16404

Table 1

Microorganisms used for Growth promotion tests (*QC of TSB (USP) 100 mL (Hy Labs Ltd; **vials containing the residual growth medium (50 mL) on day 42)

Results

- The batch of the sterilised medium used for the study has been released with a pH of 7.3, no contaminated tested container and an adequate number of colony-forming units were seen in the growth promotion test.
- No signs of microbial growth were observed in any of the 3,500 samples in total, withdrawn at days 0 (3 syringes of 5mL X 350 vials = 1,050 syringes), 14 (3 syringes of 5mL X 350 vials = 1,050 syringes) and 28 (4 syringes of 5mL X 350 vials = 1,400 syringes) during the 28-day test periods or in the residual growth media remaining in the vials.
- Microbial growth (turbidity) was observed in all inoculated positive controls (Table 2)

Microorganism	ATCC No	Reaction	Actual Colony count	Growth
Staphylococcus aureus	6538	Good	53/51	+
Bacillus subtilis	6633	Good	16/15	+
Clostridium Sporogenes	9341	Good	43/42	+
Escherichia coli	8739	Good	34/31	+
Pseudomonas aeruginosa	9027	Good	49/48	+
Candida albicans	10231	Good	40/39	+
Aspergillus brasiliensis	16404	Good	17/12	+

Table 2

Incubation conditions- Bacteria: 3 days; Fungi: 5 days; Temp. 20-25°C

Discussion

- Results of this study show that microbiological sterility can be maintained for up to 28 days and 10 activations (3 at day 1 + 3 at day 14 +4 at day 28) by using the Chemfort CSTD (Simplivia) in an uncontrolled environment, provided that the IFU of the CSTD are strictly observed.
- In clinical practice, users should be aware that working in a cleanroom environment is always advisable.
- These results are in agreement with a previous study done with the Tevadaptor CSTD (Simplivia).4 In this previous study, the physiochemical stability of 3 cytotoxic drugs was also demonstrated. The combination of these two data sets can support the extension of BUD to 28 days after first puncture in these drugs, using the Tevadaptor CSTD.
- The results of the current study are therefore just the first step in demonstrating the usefulness of vial optimization using the Chemfort CSTD, for cost reduction of drugs. To show that the Chemfort CSTD can be used for this purpose, future studies will be needed to examine the physiochemical stability of such drugs when using the Chemfort CSTD.

Conflict of Interest

RT, ASN and CNJP declare no conflict of interest related to the material presented in this article.

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