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# Evaluation of long-term prevention of microbiological contamination of sterile preparations in a controlled ISO class 5 environment and an uncontrolled environment using a closed-system drug transfer device

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**Abstract** We examined whether a closed-system transfer device (CSTD) can maintain the microbiological integrity of non-preserved single-use drug vials for an extended period beyond the approved indication for use of 7 days and 10 activations (connection–disconnection cycles) and throughout multiple withdrawals. The CSTD's ability to maintain sterility was examined in a controlled International Organization for Standardization (ISO) class 5 (European Union Good Manufacturing Practice class A) environment and a monitored but uncontrolled environment. In each environmental condition, CSTD vial adaptor units of 20-mm neck size were mounted on three hundred fifty 100-mL glass vials, each containing 100 mL of sterile tryptic soy broth growth medium. Several aliquots (5 mL) from each vial were withdrawn on days 0, 14, and 28. All syringes and the vials containing the remaining growth medium (50 mL) were incubated for 7 additional days between 20 and 25 °C, followed by 7 days between 30 and 35 °C. Incubated samples were inspected for microbial growth daily. No signs of microbial growth were observed in any of the 7,000 samples withdrawn (3,500 in each environment) during the 28-day test period or in the residual growth medium remaining in the vial after all transfers were performed. The study's findings indicate that the tested CSTD safeguards the microbiological sterility of drug preparations for up to 4 weeks after the first puncture. Once a 28-day usage period is approved by regulatory authorities, it may help avoid wasting expensive drugs.

**Keywords:** closed-system transfer device, beyond-use date, microbiological stability, drug wastage reduction



## Introduction

Closed-system transfer devices (CSTDs) use technologies to enable the reconstitution of drug powder and transfer of a drug solution into empty or prefilled containers such as syringes, bottles, or infusion bags while maintaining product sterility and protecting health care professionals from exposure to agents that are cytotoxic, mutagenic, or toxic to reproduction (so-called carcinogenic, mutagenic and reprotoxic agents).[1–3]

The performance of CSTDs in preventing exposure of health care personnel to antineoplastic drugs and antibiotics has been studied extensively.[4–11] CSTDs are usually used for preparing antineoplastic drugs for oncologic patients who are often immunocompromised. Therefore, the prepared drugs must be protected from microbiological contamination to avoid patient infections.[12–16] Whether CSTDs can prevent contamination by bacteria, yeast, mold,[17,18] and viruses[19] has been investigated in various settings.

It is generally assumed that a parenteral drug will be administered in a clinical ward immediately after it has been dissolved and/or diluted. According to a European Medicines Agency note for guidance, unpreserved sterile products must be refrigerated (2–8°C) and used for no more than 24 hours unless reconstituted or diluted under controlled and validated conditions.[20] The 2008 update of the United States Pharmacopeia (USP) Chapter 797 stated that single-dose vials opened and maintained in an ISO class 5 environment may be used for up to 6 hours after initial puncture (termed beyond-use date [BUD]) and discarded after that.[21]

However, the number of commercially available dose strengths is limited. This mainly affects antineoplastic drugs for which dosing is calculated by body weight or body surface area, and therefore, many doses do not align with manufactured vial sizes. As the required dose is mostly not equal to the amount of drug contained in the vial, some solution will be left over depending on

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the vial size and the amount used. If the number and/or frequency of patients treated with such medications is low, this results in residual unused drug solutions that must be discarded because of the lack of information on the stability of the products after their preparation, according to the Summary of Product Characteristics.

To counteract this problem and to avoid wasting expensive drugs,[22–24] multiple independent studies investigating the physicochemical stability of concentrated and diluted parenteral medicines have been conducted, very often enabling a significant extension of the BUD,[25] providing that the drug is prepared under adequate microbiological conditions. As the number of withdrawals from a single vial increases, even if the drug is physically and chemically stable, its microbiological stability becomes proportionally more important.

A previous review article summarized 12 studies that evaluated the use of CSTDs to extend the BUD. In 7 of the studies, vials were punctured with a CSTD under ISO class 5 (European Union [EU] Good Manufacturing Practice [GMP] class A) conditions. Multiple samples were collected for a maximum period of 5–14 days before incubation. In 4 of the 7 studies, no contamination was detected. In the other 3 studies, contamination was found in 0.65–1.8% of the samples. None of the studies were with the Chemfort® device.[26]

Chemfort® is unique among CSTDs in that, for pressure equalization, it uses a novel Toxi-Guard® drug-binding technology consisting of a hydrophobic membrane with 0.2-μm pores (Versapor®) and an activated carbon layer (Flexzorb™) (Figure 1). The sterility of the drug in the vial is maintained because any air entering the vial during pressure equalization passes through a hydrophobic acrylic copolymer membrane with a pore size of 0.2 μm.[7,27] While its primary purpose is to prevent the escape of hazardous drug vapors, the activated carbon layer offers additional protection against viruses, which may be small enough to pass through the hydrophobic membrane.[19] According to the Chemfort® instructions for use (IFU), the components have been demonstrated to maintain sterility for up to 7 days and 10 activations.

This study is an experimental microbiological stability study to validate the device's ability to maintain sterility under specified conditions. It is also a performance validation study for the Chemfort® CSTD (hereafter referred to as the CSTD), evaluating its capacity to extend usage duration while safely preventing contamination.

We examined whether the CSTD can maintain the microbiological integrity of nonpreserved single-use drug vials for up to 28 days and throughout multiple withdrawals under different conditions.

## Materials and methods

### *Sample size*

In this study, a sample size of 350 vials was chosen as it represents up to 3,500 preparations, depending on how often the vials are multiply used. This represents a number greater than the number of daily preparations in most standard production units.

### *Growth medium*

100 mL of tryptic soy broth (TSB) USP (lot number 1183717; expiry date: August 23, 2023) was produced and sterilized by Hylabs Ltd., Rehovot, Israel. The manufacturer's quality control was performed in accordance with the USP monograph <71> "Sterility Tests."[28]

### *Testing environment*

The ability of the CSTD to maintain a sterile barrier was tested in two environments: (1) a controlled ISO class 5 (EU GMP class A, laminar air flow hood in a class B room) environment in a GMP-licensed compounding pharmacy and (2) an uncontrolled but monitored environment in a standard shipping container of 2.5 meters (8 feet) × 6 meters (20 feet).

To determine the potential exposure to microorganisms during all manipulations and verify the controlled or uncontrolled classification of the environment, air quality was monitored continuously for particles with a Solair Airborne Particle Counter 3100 (Lighthouse Worldwide Solutions, Medford, OR), actively for colony-forming units (CFUs) of microbes with an Air IDEAL® 3P Aerobiocollector (BioMérieux SA, Marcy-l'Étoile, France) and also passively with CASO-Agar 90 mm isolator clean room+ settle plates (Merck-Millipore; catalogue number 1466850120; lot number 792879). [29,30] The number of permitted airborne particles during the study was classified according to EU GMP Guidelines, Annex 1. [31]

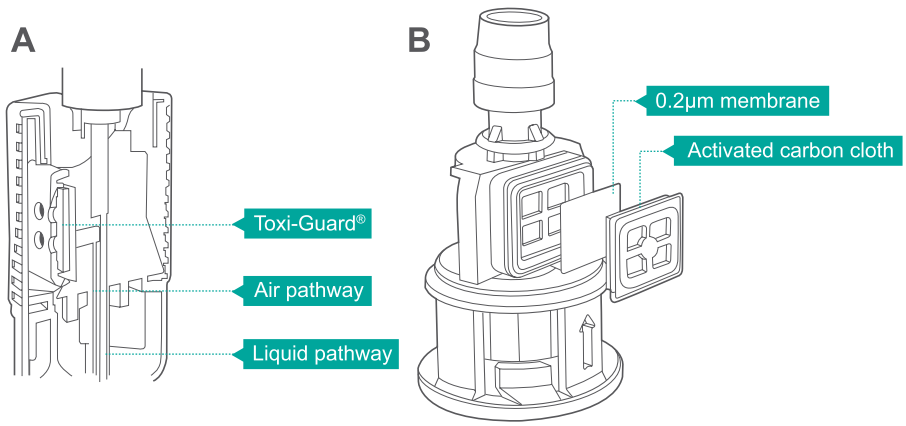


**Figure 1.** Chemfort® Toxi-Guard® structure: (A) cross-section of the Chemfort® Vial Adaptor; (B) Toxi-Guard® component of the Chemfort® Vial Adaptor.

### *Testing procedure*

This study was conducted from February 03, 2022, to May 12, 2022.

In each environment, the CSTD was handled as described in the device's IFU.[32]

20-mm units of the Chemfort® Vial Adaptor (Simplivia Healthcare Ltd., Kiryat Shmona, Israel; lot number: UAF516; expiry date: September 30, 2023) were assembled onto three hundred fifty 100-mL 20-mm neck-size glass vials, each containing 100 mL of the sterile TSB growth medium (Figure 2). Before accessing it, the rubber stopper of the vial was disinfected with 70% isopropyl alcohol (IPA) pads (Quickpads, Holtsch Medizinprodukte GmbH, Taunusstein, Germany; lot number: 110421; expiry date: March 2023) with an intense circular motion for not <5 seconds and under maintenance of the minimum exposure time of 15 seconds according to the IFU of the IPA pads. In addition to the requirements of the IFU, we strictly followed good aseptic preparation practices in general. There are different ways to handle the connection process of the CSTD syringe adaptor lock (Simplivia Healthcare Ltd.; lot number: UAF518; expiry date: September 30, 2024) to the 10-mL sterile syringe (Omnifix® Luer Solo, B. Braun Austria GmbH, Maria Enzersdorf, Austria; lot number: 21K27C8; expiry date: September 01, 2026). In this study, we used the following procedure: (1) components were touched only on the outside of the primary packaging; (2) gloves were disinfected every 10 minutes; (3) all devices were kept horizontal during steps 4–6; (4) the primary packaging of the syringe adaptor lock was peeled open half-way; (5) the primary packaging of the Luer lock syringe was peeled off from the plunger end; (6) the syringe adaptor lock was immediately connected to the syringe, keeping the exposure time and the corresponding risk of microbiological contamination to a minimum.

On days 0, 14, and 28, 5-mL aliquots (3 aliquots on days 0 and 14 and 4 aliquots on day 28) were withdrawn from each vial by attaching a CSTD syringe adaptor lock to the vial adaptor and then withdrawing the medium using the 10-mL sterile syringe. Each time a syringe with a connected syringe adaptor lock was attached to the vial adaptor of the TSB vial, septa of both the vial adaptor and the syringe adaptor lock were also wiped with 70% IPA according to the IFU and allowed to dry. The syringe adaptor lock was left on the syringe, capped, and incubated for 7 days in a constant climate chamber (Model Klimaprüfung mit Befeuchtung [KBF] P 720, Binder GmbH, Tuttlingen, Germany) between 20 and 25 °C (climate chamber set to 22.5 °C), visually inspected daily for microbial growth, and then incubated between 30 and 35 °C (climate chamber set to 32.5 °C) for 7 additional days, with daily observations for microbial growth. Following the withdrawal of the final sample on day 28, the vials containing the remaining growth medium (50 mL) were incubated and examined according to the same procedure. The incubation was performed sequentially in two temperature ranges (20–25 °C for yeast and mold and 30–35 °C for bacteria), to increase specificity for the growth conditions for yeast, mold, and bacteria. The conditions (dual incubation protocol[33,34]) selected are optimal for recovery and for allowing detection of both slow- and normal-growing organisms (i.e., adequate to detect microorganisms that might otherwise be difficult to culture).

Following the incubation, on day 42, the growth-promoting capability of the medium was tested by inoculating 10 containers with each of the seven test microorganism strains, according to European Pharmacopoeia[35] (50 containers total). The positive control required microbiological growth from minimum inoculum (10–100 CFUs) to be observed in all test containers.

Sterility evaluation following the use of the CSTD in an uncontrolled environment followed precisely the same steps described above. However, the environment was worse than EU GMP class D (ISO class 8), as observed by continuous particle monitoring.

### *Evaluation of contamination*

At each time point, microbial contamination in both test syringes and test vials fitted with CSTD adaptors was evaluated visually for turbidity of the growth media, using a backlight.

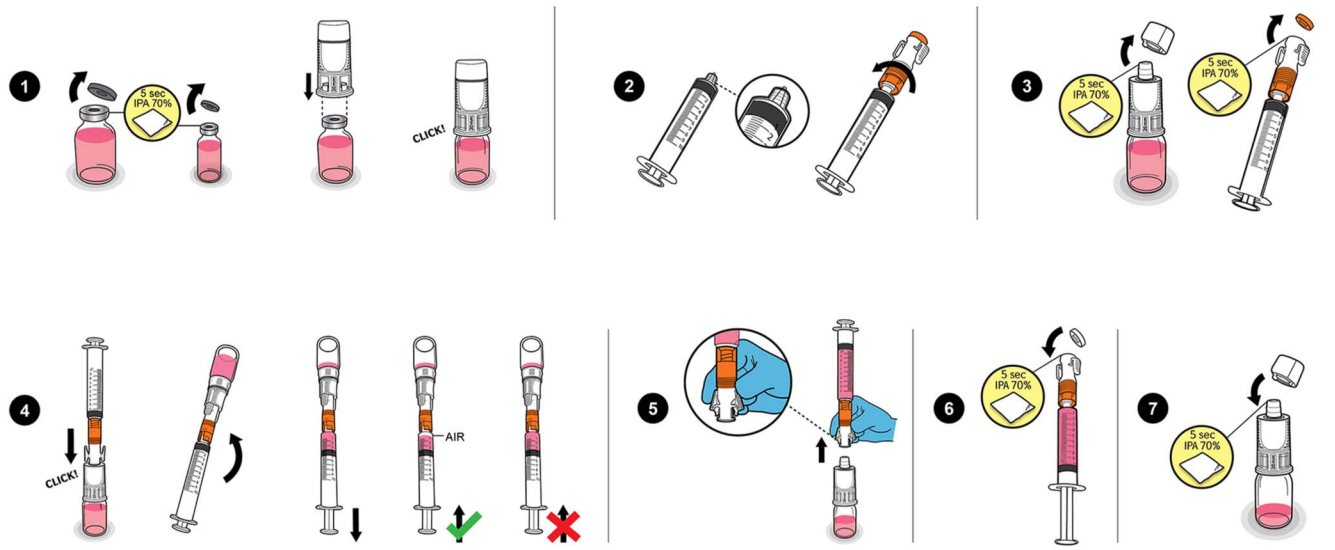


**Figure 2.** CSTDs were handled as described in the device's IFU: (1) Before attaching the vial adaptor, the rubber stopper of the vial containing 100 mL of sterile TSB growth medium was disinfected with 70% IPA with an intense circular motion for not <5 seconds and under maintenance of the minimum exposure time of 15 seconds. (2) The syringe adaptor lock was connected to the Luer lock syringe. (3) Each time a syringe with a connected syringe adaptor lock was attached to the vial adaptor of the TSB vial, the septa of both were wiped with 70% IPA and allowed to dry. (4, 5) The syringe adaptor lock was used to withdraw aliquots of TSB, according to the CSTD IFU. (6, 7) Sterile caps were replaced on the syringe adaptor lock and the vial adaptor during incubation.

## Results

No signs of microbial growth were observed in any of the 3,500 samples withdrawn on days 0 (3 syringes of 5 mL per vial = 1,050 syringes), 14 (3 syringes of 5 mL per vial = 1,050 syringes), and 28 (4 syringes of 5 mL per vial = 1,400 syringes) during the 28-day test period or in the residual growth medium remaining in the vial after all transfers were performed in either the controlled or the uncontrolled environment (7,000 syringes and 700 vials total for both environments). Microbial growth (turbidity) was induced in all inoculated positive controls.

In the uncontrolled environment, values during continuous microbiological contamination measurement ranged from 210 CFU/$m^3$ (air samples)/105 CFU/4 hours (settle plates)/53 CFU/plate (contact plates) to 322 CFU/$m^3$/159 CFU/4 hours/76 CFU/plate, respectively, which is above the upper limit for microbial contamination allowed in an EU GMP cleanroom class D environment.[31] The average number of particles per cubic meter of sizes $>0.5$ μm and $>5$ μm was continuously high during operation (although no upper limit for EU GMP class D is predetermined): 6,321,252 (4,538,202–8,107,945) and 41,808 (38,903–43,908), respectively.[31]

## Discussion

Theoretically, no contamination should occur under ISO class 5 conditions, even without a CSTD. Studies in a review article that included conventional (no CSTD) comparators also demonstrate this.[26] However, incorrect working procedures or transient failure of the cleanroom controls may present a risk of contamination.

This study showed that the tested CSTD safeguards the microbiological sterility of drug preparations for up to 4 weeks, even if manipulations are performed under conditions of high bioburden, as long as a state-of-the-art preparation technique and the device's operating instructions are strictly observed. In contrast to the review article of Sobieux et al,[26] this study found no contamination when using the CSTD, despite extension of observation time to 28 days. This was in line with the results of 3 of 7 studies that used CSTDs mentioned in the review article.

### *Possible reasons for detected contamination in other studies*

Some of the reviewed studies encountered contamination, and our findings help shed light on possible reasons. Handling errors and external contamination were frequently identified as sources of microbial presence in vials, emphasizing that even with CSTDs, improper handling techniques or environmental exposure can introduce contaminants. In addition, noncompliance with sterile preparation standards may have contributed to these contamination cases. Noncompliance with such standards, which are designed to minimize microbial risks, often leads to a higher rate of contamination.

Furthermore, conflicts of interest were reported in seven studies associated with CSTD manufacturers. This factor introduces potential bias, whether intentional or unintentional, potentially influencing study design, execution, or interpretation in favor of positive outcomes for specific CSTDs.

The lack of comparator groups in nine studies also limits our understanding of how CSTDs perform relative to conventional methods. Without a comparator, it is challenging to assess whether contamination could be ascribed to the CSTD or other procedural factors.

Some studies also suffered from inadequate reporting and study design elements, including unclear design protocols, setting descriptions, participant details, and assessments of bias risk. Such deficiencies could skew results, potentially underestimating contamination sources.

Last, environmental factors varied across studies conducted in different countries and settings, introducing variability in aspects such as air quality and cleanliness in compounding areas, which could influence contamination rates observed across studies.

### *Strengths of the tested device in contamination prevention*

The device evaluated in our study demonstrated robust performance in preventing contamination, supported by its dual-membrane barrier system (Figure 1), which provides protection even during potential technical failures in controlled environments. Typically, drugs in preparation during such failures would need to be discarded, incurring significant costs. However, this study suggests that using the tested device could help avoid these costs by maintaining sterility despite minor environmental lapses.

The large sample size and repeated withdrawals performed in an uncontrolled environment without any observed microbial growth underscore the tested CSTD's potential in contamination prevention. Uncontrolled environments inherently have unknown degrees of bioburden,[34,36,37] yet our results indicate that the tested CSTD can mitigate contamination risks when used with meticulous technique. This finding is especially valuable for situations where cleanroom conditions may not be feasible, such as drug preparation in hospital wards, as the CSTD seems to maintain sterility even outside ideal conditions.

### *Importance of skilled handling and environment selection*

While this study suggests that the tested CSTD may allow the extension of BUDs to 28 days after the first puncture, users should recognize that the best environment for drug preparation remains a cleanroom, as it provides a dual safety system to further reduce contamination risks. Nevertheless, the effectiveness of microbiological safety depends not only on the environment but also significantly on user skill and adherence to proper technique. Errors in handling or improper technique may lead to contamination, even with advanced CSTDs.[38,39] Thus, the findings apply only under conditions of strict adherence to proper working techniques, performed by well-trained staff, and accompanied by thorough risk assessment.

### *Study limitations and applicability*

The results of this study are specific to the Chemfort® CSTD. Using other CSTDs under identical conditions may produce different outcomes due to variations in device design and performance. Therefore, the findings should not be generalized across all CSTDs but instead interpreted within the context of the tested CSTD's specific features and capabilities.

The study focuses on microbiological contamination, but it does not address other potential long-term effects of using the CSTD, such as the physical or chemical stability of drugs, which are also critical for extending BUD.

### *Practical suggestion*

We suggest that separate studies should be conducted under similar conditions but in different environments to further

support our findings. If possible, these studies should involve comparison groups (such as traditional systems, without CSTDs). This will help verify the advantages observed with the tested device. By reinforcing the existing evidence through replication efforts, decisions regarding prolonging expiration dates can be made with higher confidence.

## Conclusion

In conclusion, the findings of this study indicate that Chemfort® safeguards the microbiological sterility of hazardous drug preparations for up to 28 days after the first puncture even if manipulations are performed under conditions of high bioburden. Thus, once a 28-day usage period for the vial adaptor is approved by regulatory authorities, this CSTD may help to avoid wasting expensive drugs, particularly in cases where environmental control may be temporarily compromised.



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