The use of closed-system transfer devices (CSTDs) for compounding hazardous medications has become an accepted standard of practice to minimize environmental exposure to these agents. It has been reported that CSTDs can also preserve the sterility of unpreserved (single-use) medication vials. Maintaining sterility for prolonged periods may result in significant cost-savings through reduced drug waste. In a study of the cost-savings from using the PhaSeal CSTD (Becton, Dickinson and Company, Durham, NC) to extend the beyond-use date (BUD) of single-use vials, the potential savings were estimated to be $600,000 annually for 1 institution. A study of the actual savings achieved by using PhaSeal to extend the BUD of single-use vials demonstrated savings of $96,348.70 in <2 months, representing an annual saving of $703,047.67. In addition, using a CSTD to preserve the sterility of vials of parenteral medication may assist pharmacists in managing shortages of such drugs. Medication shortages can have an adverse impact on patient health. Of the 183 drug shortages reported in August 2015, 105 (57%) were of parenteral medications. Extending the BUD of parenteral drugs that are available in single-use vials is a significant cost savings for parenteral medications.

Background: US Pharmacopeia (USP) Chapter 797 states that single-use vials may be used within 6 hours of initial puncture if maintained in an International Organization for Standardization 5 environment. The 6-hour standard is based on the microbial growth observed in various growth media under conditions specified in USP Chapter 71. However, studies have demonstrated that the PhaSeal closed-system transfer device (Becton, Dickinson and Company, Durham, NC) maintains sterility of unpreserved, single-use vials for ≤7 days. In these studies, the PhaSeal system was tested using growth media under simulated conditions. Extending the beyond-use date (BUD) of medications could reduce expenditures for medications, and help pharmacists cope with shortages of critical medications.

Objective: The purpose of this study was to confirm these results in actual practice, using an anti-neoplastic agent as the test solution.

Methods: In this prospective, observational study, fluorouracil aliquots were transferred to tryptic soy broth culture medium in intravenous bags over a 2-week period, using the PhaSeal system. Twelve aliquots and 96 bags were used. The bags and their contents were stored at 35°C for 14 days, and were monitored for evidence of microbial contamination.

Results: No microbial growth was observed throughout the 14-day period. Thus, at 336 hours (14 days), the probability of failure was 0% (95% confidence interval, 0-0.033).

Conclusion: The PhaSeal system maintains the sterility of unpreserved injectable solutions and can apparently be used to extend the BUD of single-use vials to ≥7 days. Findings support those of previous studies of PhaSeal’s utility in the reduction of medication waste, and the realization of significant cost savings for parenteral medications.
Determination of Extended Sterility for Single-Use Vials

According to US Pharmacopeia (USP) Chapter 797, single-use vials must be used within 6 hours of being opened if maintained in an International Organization for Standardization (ISO) 5 environment, or within 1 hour if in a non-ISO 5 environment. The 6-hour standard is based on microbial growth observed in various growth media under conditions specified in USP Chapter 71, and aims to prevent patient harm by minimizing the impact of any microbial contamination. However, this standard was not established by direct testing of unpreserved vials under conditions of actual or simulated practice.

Specifically, USP Chapter 797 states that single-use vials exposed to an ISO 5 environment "...may be used up to 6 hours after initial needle puncture," implying that a nonpreserved vial maintained in this environment could be used >1 time. This chapter also specifies that the BUD must be assigned "on the basis of direct testing or extrapolation from reliable literature sources and other documentation." Strictly limiting the BUD to 6 hours can cause significant waste of costly medications or critical agents with limited availability. However, if a CSTD can maintain sterility of unpreserved vials for longer periods, it may be possible to extend the BUD of those vials. If using such a device ensures the sterility of these drugs so that all the contents of the vial can be used without harming the patient, then overall drug waste could be reduced substantially. Use of a CSTD to extend the BUD has been suggested to minimize the impact of drug shortages, as well as medication waste, and can result in significant cost-savings.

A CSTD could potentially block the transfer of contaminants into the system, and, thus, maintain sterility of the medication. In a comparison study of 4 CSTDs, De Prijck and colleagues contaminated the protective coupling component (ie, injector or inlet) of each CSTD, and the rubber stoppers of vials with microorganism inoculation, and measured microbial contamination of the vials after multiple entries into each vial. All 4 systems demonstrated evidence of contamination if the vial stopper was not disinfected properly. Among the systems tested, PhaSeal was the most resistant to microbial contamination of the vial after repeated entries.

Several studies have shown that the PhaSeal system maintains sterility of single-use vials for ≤7 days. McMichael and colleagues noted a contamination rate of 1.8% (6 of 332 samples) during the 168-hour study period; therefore, the probability that the vials would not be contaminated for ≥168 hours is 98.2%. Carey and colleagues reported a contamination rate of 0.3% during 168 hours, and an expected 99.7% probability that the vial would not be contaminated if manipulated by the same procedures, under the same environmental conditions. Rowe and colleagues reported an overall contamination rate of 1.86% (11 of 592 samples had 1 colony-forming unit [cfu] on sheep blood agar or trypticase soy agar plates) for their 14-day study period. These studies were performed using sterile culture media under simulated conditions, or involved transfer of antineoplastic agents in an open system having greater potential for contamination. Although these studies were relatively small, the results were sufficient enough to convince the US Food and Drug Administration (FDA) to grant the ONB (Closed Antineoplastic and Hazardous Drug Reconstitution and Transfer System) product code to the PhaSeal system. The ONB product code is assigned to devices that have been certified as closed-system transfer units for use in compounding antineoplastic agents and other hazardous drugs. The code is awarded based on satisfying ≥2 of 3 criteria, which require the product to be leakproof (ie, no escape of hazardous drug or vapor concentration; no transfer of environmental contaminants), airtight, and preventive against microbial ingress.

The criteria used by the FDA to make this determination were: “no transfer of environmental contaminants,” and “prevention of microbial ingress.”

Awarding of the ONB code to PhaSeal, coupled with evidence of the system’s effectiveness in preventing contamination and maintaining sterility of unpreserved single-use vials for ≤7 days, suggest that PhaSeal can be used to extend the BUD of medications without increasing the safety risk for patients. However, a limitation of the studies that show PhaSeal’s ability to maintain sterility is the test conditions, which were artificial.

The purpose of the current study was to test the effectiveness of the PhaSeal system in actual practice, using an antineoplastic agent as the test solution. Sterility monitoring was used as a measure of quality assurance for our compounding procedures.

Methods

All tests were performed in the hematology-oncology pharmacy, in ISO 5 conditions using class II, type B2 biological safety cabinets (BSCs) and personal protective equipment, in compliance with all requirements of USP Chapter 797. The BSCs were certified according to NSF/ANSI-49 specifications to ensure compliance with USP Chapter 797 requirements. All PhaSeal devices were attached in accordance with the manufacturer’s instructions in the ISO 5 cleanroom.

Hands were washed, and sterile gloves were donned and sanitized prior to work in the BSC. The PhaSeal protector, adapter, and injector were placed in the BSC. In accordance with USP Chapter 797 standards, the work surface, syringes, intravenous (IV) bags, fluorouracil vials, and PhaSeal components were sanitized with
sterile, 70% isopropyl alcohol before being placed in the BSC. Labels consecutively numbered with “0 hours, vial number” were affixed to the front of each 100-mL tryptic soy broth (TSB) IV bag. Matching numbered labels were affixed to 100-mL fluorouracil and positive control vials or sample vials. The IV bags, vials, and equipment were placed in the BSC by an assistant, which precluded the operator from having to remove his or her hands from the BSC; this expedited the test process. The assistant also placed new test materials in the BSC, and removed used bags and storage vials. The operator resanitized his or her gloved hands after every 3 preparations, or whenever he or she touched items outside the BSC.

The TSB bag was placed on the work surface. The cap was removed from the matching numbered 100-mL fluorouracil vial. The vial septum was sanitized by wiping once with sterile, 70% isopropyl alcohol from the septum across the aluminum rim, in a unidirectional motion. The alcohol was allowed to dry for ≥ 10 seconds. The PhaSeal protector was removed from its wrapper aseptically by touching only the expansion bell or cap. The injection port remained sterile. The cap of the PhaSeal protector was aseptically removed from the device, and the protector was attached to the vial. The cap covering the set port of the IV bag was removed, and the port was sanitized with sterile, 70% isopropyl alcohol. A PhaSeal infusion adapter was aseptically removed from its sterile packaging and inserted into the port on the TSB bag. Ten mL of air were drawn into a 20-mL syringe, to which the PhaSeal injector was attached. The syringe-injector combination was attached to the vial-protector combination, and was attached to the port on the infusion adapter, which had been attached to the TSB bag. The contents of the syringe were injected into the TSB bag. The injector-syringe assembly was disconnected from the infusion adapter–IV bag assembly and discarded.

The protector-fluorouracil vial combination was placed in an amber plastic bag for light protection, and stored in the ISO 5 room to minimize contamination. The procedure was repeated at 6 hours, and on days 1 (24 hours), 2 (48 hours), 3 (72 hours), 5 (120 hours), 7 (168 hours), and 14 (336 hours). The TSB bags containing fluorouracil or a positive control were incubated at 35°C for 14 days, and monitored daily for evidence of microbial contamination based on the appearance of turbidity.
A total of 12 fluorouracil vials were tested among 96 TSB bags. The 2 positive controls were Staphylococcus aureus 6538 and Escherichia coli 25922 (each 100 cfu/mL, obtained from the American Type Culture Collection). Two unopened TSB bags served as negative controls.

Results

No evidence of microbial contamination was noted in any test sample (Table). This indicates that, at 336 hours (14 days), the probability of failure (ie, contamination) was 0% during the transfer of fluorouracil to TSB IV bags (95% confidence interval, 0-0.033).

The TSB culture bags were inoculated with 1 mL of the organism, and incubated at 35°C. The 2 negative controls showed no visual evidence of microbial contamination or turbidity after 72 hours, or at 14 days of incubation (Table). The positive controls showed growth at 48 hours. Crystallization was observed in 4 of the 12 fluorouracil vials after 1 week of storage at 22°C. The crystallization was attributed to a lower-than-usual room temperature, and not believed to be related to the sterility of the preparations or testing procedure.

Discussion

Our findings support the notion that the PhaSeal system maintains the sterility of parenteral solutions and allows extension of the BUD of single-use vials to ≥7 days. Our results are similar to those of McMichael, Carey, and their respective colleagues, who demonstrated that PhaSeal is capable of maintaining sterility of single-use vials in a controlled environment for ≤168 hours.3,4

Although our study was based solely on sterility findings, the chemical stability of the drug must also be considered. If a drug’s chemical stability is limited, the ability to extend the BUD will be limited as well. For example, solutions of cyclophosphamide reconstituted with saline (20 mg/mL) are stable for 6 days if refrigerated at 2°C to 8°C.12 Even though the PhaSeal system would maintain the sterility of the solution for 7 days, any unused cyclophosphamide solution would need to be discarded after 6 days. Conversely, commercially available fluorouracil solutions (50 mg/mL) typically have expiration dates of ≥1 years. In our study, sterility was assessed for only 14 days; therefore, based on our findings, the BUD for fluorouracil should not exceed 14 days. Additional studies are warranted to confirm our results and examine whether sterility could be maintained for a longer period.

Despite our findings, we recommend a BUD of 7 days, as previously reported.13 Although Martel and colleagues reported that the stability of fluorouracil in polyvinyl chloride bags is unaffected through 14 days of storage at 4°C or 21°C, they found visual evidence of flocculent precipitate in several vials after 5 days of storage in an ISO 5 environment.13 Heating (to 60°C) and vigorous shaking of the vial often dissolves the precipitate.14 A potential confounding factor would be any antimicrobial activity of the fluorouracil itself. Some antineoplastic agents may exhibit low-level activity against indigenous human microflora, and/or opportunistic pathogens.15,16 This antimicrobial activity is not directed against any specific microbial agent,15 and is unlikely to preclude the recovery of bacteria by standard culture techniques.16

Limitations

The major limitations of our study are the small sample size, use of only 1 culture medium, visual determination of contamination, and testing of only 1 drug. The small sample size did not provide sufficient power to detect possible statistical differences or significance, potentially leading to a type II error (false-negative result). Because only 1 culture medium was used, detection of contamination was limited to organisms that can grow in that particular medium. Our findings for fluorouracil may not reflect the stability of other drugs subjected to similar conditions.

Determining contamination by visual inspection may be inferior to inoculating and incubating plates of growth media. Visual examination was chosen over plating for 2 reasons: we desired to maintain a completely closed system to eliminate any possibility of an additional source of contamination, which might confound our results, and did not have support from the microbiology laboratory for processing samples of a hazardous agent. Based on our findings, we recommend routine monitoring of sterility in partially used vials by sampling the contents during and after compounding sterile dosage forms of medications.

Conclusion

Under conditions that resemble an actual practice setting, it appears that the PhaSeal system maintains the sterility of parenteral solutions, and allows extension of the BUD of single-use vials to ≥7 days. This supports previous recommendations for using the PhaSeal system to reduce the impact of drug shortages, decrease medication waste, and significantly increase cost-savings. ■

Author Disclosure Statement

Dr Ho, Mr Solimando, and Mr Johnson reported no conflicts of interest; Dr Edwards is on the Speakers Bureau for Celgene, Millennium, SeattleGenetics, Merck, Astellas, and Onyx.

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