The use of a closed-system transfer device (CSTD) has been accepted as a standard of practice to minimize exposure to harmful materials when compounding hazardous medications.1 Several reports indicate that CSTDs also preserve the sterility of unpreserved (ie, single-use) medication vials for up to 1 week.2-5 Taking advantage of prolonged sterility of unpreserved vials with an appropriate CSTD attached offers the possibility of significant cost-savings through reduced drug waste.1,6

The cost of healthcare continues to rise in the United States; healthcare costs were estimated to be more than $3 trillion in 2016, and pharmaceuticals are estimated to account for approximately 10% (> $300 billion) of the total cost of healthcare.7 In 2017, the

Sterility Duration of Single-Use Vials for Antineoplastic Agents or Monoclonal Antibodies Extended with a Closed-System Transfer Device

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BACKGROUND: Pharmaceuticals are a large component of the healthcare system. The cost of drugs continues to rise every year, especially intravenous antineoplastic agents and monoclonal antibodies. Extending the beyond-use date of nonpreserved vials of antineoplastic agents allows them to be used in multiple preparations, which has been shown to save costs. Studies of closed-system transfer devices (CSTD) usually focus on reducing exposure to hazardous materials. Data on maintaining the sterility of single-use vials beyond-use date with the use of a CSTD are limited.

OBJECTIVES: To validate in actual practice in a hematology-oncology pharmacy the internal 7-day beyond-use date for unpreserved vials of antineoplastic agents that are known to be chemically stable for at least 7 days, and to assess if they could remain stable for up to 15 days.

METHODS: We performed a real-time collection and validation of the sterility of single-use vials of antineoplastic agents between March 2015 and June 2015. Drugs in nonpreserved, single-use vials that had at least 1 mL of liquid and had a CSTD (ie, the PhaSeal system) adaptor attached, were collected at day 8. All vials had been used at least once for regular preparation of antineoplastic doses dispensed to patients to verify sterility after actual practice manipulation of the CSTD and the vials. Two 0.5-mL samples were tested in a thioglycollate broth and in a tryptic soy broth separately. Each sample was then incubated for 15 days. On day 15, 2 additional 0.5-mL samples were removed from the vials and were sampled in a thioglycollate broth and in a tryptic soy broth.

RESULTS: A total of 50 vials with a CSTD were collected during the 4-month study period. This included 18 different cytotoxic agents and 4 monoclonal antibodies. Two samples of 1 drug, carfilzomib, tested positive for microbial growth on day 8. Further testing suggested that these were false-positive findings, which were caused by a reaction of the drug to the growth media.

CONCLUSION: Our findings show that when compounding hazardous medicines, the use of a CSTD, such as the PhaSeal system, can maintain sterility in nonpreserved single-use vials for 7 days, and extend their beyond-use date for a minimum of 15 days.

Disclosures are at end of text

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The data in this study were presented as a poster at the Hematology/Oncology Pharmacy Association annual meeting at Austin, TX, March 25-28, 2015.
global cost of oncology-related medications was approximately $133 billion and approximately $50 billion in the United States. Over the next 5 years, the cost of oncology medications in the United States is anticipated to increase to approximately $100 billion.8

Between 2012 and 2013, the US Food and Drug Administration (FDA) reported a shortage of 12 parenteral antineoplastic drugs.9 Although the number of injectable antineoplastic drug shortages was reduced to 4 at the time this article was written, shortages of appropriate medications continue to be a problem.9 Such shortages adversely affect the selection of appropriate therapy, research study design, and patient care.

In a survey conducted in 2012 and 2013 by Kehl and colleagues for the Cancer Care Outcomes Research and Surveillance Consortium, a total of 330 oncologists caring for patients with lung or colorectal cancer responded.10 Of the responding oncologists, 74% reported having experienced a pharmaceutical shortage, and 28% changed therapy to a less than desirable regimen because of drug shortages.10

Antineoplastic agents that have been in short supply in recent years include Tice BCG, cisplatin, cytarabine, doxorubicin powder, etoposide, fluorouracil, methotrexate, mitomycin, and paclitaxel.10-13 In 2013, the American Society of Health-System Pharmacists conducted a survey about shortages of injectable oncology drugs and the impact on patient care.14 Overall, 99% (211 of 214) of respondents reported at least 1 shortage in the previous 12 months, and 62% reported using alternate drug regimens because of shortages. The strategies used by survey respondents included drug dosage changes, delays of treatment, and patient referrals to or from other facilities.11

The use of a CSTD is the standard practice for compounding sterile forms of hazardous agents. A CSTD limits occupational exposure to hazardous drugs, and it also decreases the amount of drug that must be properly disposed of as a hazardous material.14,15 The US Environmental Protection Agency oversees the disposal of hazardous waste, including antineoplastic drug therapies.16 The Resource Conservation and Recovery Act limits the hazardous waste to less than 3% from “cradle-to-grave,” including generation, transportation, treatment, and storage through disposal of hazardous waste.16 Residual amounts of more than 3% of hazardous pharmaceuticals, such as chemotherapy in vials, require a mechanism for storage, transportation, and manifest for disposal to a permitted facility.17

The US Pharmacopeia Chapter 797 (USP 797) mandates that single-use vials be used within 6 hours of opening, if maintained in an International Organization for Standardization (ISO) 5 environment, or within 1 hour in a non–ISO 5 environment.18 Before the 2016 revision, the chapter implied that nonpreserved vials maintained in an ISO 5 environment could be used more than once *based on data from direct testing or extrapolation from reliable literature sources and other documentation.*18

De Prijck and colleagues contaminated with microorganisms the injector component of 4 different CSTDs (including Clave Connector, Chemoprotect Spike, PhaSeal, and Securmix) and the rubber stoppers of vials, then measured the microbial contamination after multiple entries into each vial.2 The 4 systems showed evidence of contamination if the vial stopper was not properly disinfected before entry. When the stopper was disinfected correctly, the PhaSeal CSTD was most successful among the 4 CSTDs in preventing microbial contamination after repeated entries.2

Other studies indicate that the PhaSeal CSTD maintains sterility in nonpreserved vials for up to 168 hours.3-5 McMichael and colleagues reported a contamination rate of 1.8%, and a probability of 98.2% that the vials would remain sterile for up to 168 hours.3 Carey and colleagues reported a contamination rate of 0.3%, and a 99.7% probability that the vial would remain sterile using similar procedures and environmental conditions.4 Rowe and colleagues reported that 1.86% of the samples had 1 colony-forming unit on sheep blood agar or on trypticase soy agar plates.5

The results of these small studies have been included in the evidence submitted to the FDA to grant the ONB (closed antineoplastic and hazardous drug reconstruction and transfer system) product code to some of the available CSTDs (including PhaSeal).19 The ONB product code is assigned to CSTDs for compounding hazardous drugs. The ONB code was given based on the understanding that the CSTD is leakproof (ie, has no escape of hazardous drug or vapor concentration, and no transfer of environmental contaminants); airtight; and prevents microbial ingress.19

The reports by De Prijck, McMichael, Carey, Rowe, and the FDA ONB code, substantiate the use of a CSTD to extend the beyond-use date of medications without compromising patient safety.2,5,19

Rowe and colleagues used a theoretical model to estimate potential reduction in drug expenditures by using the PhaSeal system to extend the beyond-use date past 6 hours. Their model estimated an annual saving to their institution of more than $600,000.5 Edwards and colleagues found a cost-savings with the PhaSeal system of more than $96,000 during the 50 days of data collection, which they estimated to represent an annual saving of more than $700,000.6 They also reported that the use of this CSTD decreased drug
waste of nonpreserved vials by more than 50%.6

Ho and 2 of the current authors (Edwards and Solimando) tested vials of fluorouracil to demonstrate prolonged sterility after the attachment of a PhaSeal adaptor.20 Intravenous bags of tryptic soy broth (TSB) culture medium were inoculated with fluorouracil from previously unopened vials and incubated at 35°C for 14 days in the ISO 5 room. No growth was seen during the monitoring period.20

A significant limitation of all these previous studies was the simulated test conditions used. In the current study, we expanded our previous work,20 by instituting sterility monitoring using a practice-related procedure as a quality assurance measure for our compounding procedures. In the current study, we used test vials that had been used multiple times for compounding sterile medications in the hematology-oncology pharmacy. To our knowledge, this is the first report of testing vials used in actual practice rather than in an artificial test environment. The purpose of the current study was to determine if the sterility of nonpreserved vials with a PhaSeal CSTD attached was maintained for up to 7 days when used in actual compounding procedures in the pharmacy. We also assessed if sterility can be maintained for up to 15 days.

**Methods**

USP Chapter 71 (USP 71) recommends the use of fluid thioglycollate medium and TSB for sterility testing.21 Under optimal conditions, thioglycollate will allow growth of anaerobic and of aerobic bacteria.22,23 TSB, also known as soybean-casein digest, is a medium for growing fungi and aerobic bacteria.22

Our study design used the parameters for sterility testing described in USP 71.21 We developed a list of nonpreserved antineoplastic agents, including monoclonal antibodies, as shown in Table 1.

A PhaSeal adaptor was attached to each single-dose vial. Medications with a chemical stability of less than 7 days were considered expired when the chemical stability was reached, and all other vials were considered expired 7 days from the initial entry. We stored opened vials under refrigeration (2°C to 8°C) or at room temperature (20°C to 25°C), as recommended in the drug’s product information. When another dose for the drug was ordered, the opened vial was retrieved, and the appropriate dose withdrawn. At the end of day 7, vials with at least 1 mL of remaining solution were used for testing.

Two 0.5-mL aliquots of the drug were withdrawn from the vial into 2 separate 1-mL syringes. Each aliquot was assigned a study number. The study number and the drug’s name, concentration, manufacturer, and lot number, as well as the drug’s expiration date were recorded. The aliquots were labeled with the study number and the day (day 8 or 15).

Upon initial use, the technician or the pharmacist preparing the dose attached a PhaSeal adaptor to each vial in a class II, type B2, biological safety cabinets in the hematology-oncology pharmacy ISO 5 environment, using appropriate aseptic techniques. Each vial was labeled with the date it was opened; beyond-use date, with a maximum of 7 days; and the technician’s or the pharmacist’s initials. If necessary, the drug was reconstituted according to the pharmacy’s standard procedure. The appropriate dose was withdrawn from the vial. The test vials were collected over a 4-month period, from March 2015 through June 2015.

Partially used vials that were to be saved for reuse were stored at room temperature (20°C to 25°C) or under refrigeration (2°C to 8°C), as recommended in the drug’s product information. When another dose for the drug was ordered, the opened vial was retrieved, and the appropriate dose withdrawn. At the end of day 7, vials with at least 1 mL of remaining solution were used for testing.

The blinded samples were then delivered to the microbiology department for direct inoculation of TSB and thioglycollate broth. Each inoculate was labeled with the assigned number attached to the sample. The drug was inoculated into 2 separate 1-mL syringes. Each aliquot was assigned a study number. The study number and the drug’s name, concentration, manufacturer, and lot number, as well as the drug’s expiration date were recorded. The aliquots were labeled with the study number and the day (day 8 or 15).

The blinded samples were then delivered to the microbiology department for direct inoculation of TSB and thioglycollate broth. Each inoculate was labeled with the assigned number attached to the sample. The samples were incubated for 14 days, as described above.

In the microbiology laboratory, 10 mL of commer-

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**Table 1 Mediations in Single-Dose Vials Identified for Study Inclusion**

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
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<tbody>
<tr>
<td>Belimumab</td>
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<td>Obinutuzumab</td>
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<td>Bevacizumab</td>
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<td>Panitumumab</td>
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<td>Brentuximab</td>
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<td>Pembrolizumab</td>
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<td>Cetuximab</td>
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<tr>
<td>Ramucirumab</td>
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<td>Ipilimumab</td>
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<td>Rituximab</td>
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<table>
<thead>
<tr>
<th>Antineoplastic agents</th>
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<tbody>
<tr>
<td>Bendamustine</td>
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<td>Epirubicin</td>
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<td>Bleomycin</td>
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<tr>
<td>Fluorouracil</td>
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<td>Bortezomib</td>
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<td>Carfilzomib</td>
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<td>Carmustine</td>
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<td>Clofarabine</td>
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<td>Oxaliplatin</td>
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<td>Cyclophosphamide</td>
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<td>Pegasparginase</td>
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<td>Doxorubicin</td>
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<tr>
<td>Doxorubicin liposomal</td>
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<tr>
<td>Doxorubicin liposomal</td>
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</tbody>
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cially available thioglycollate (Renek lot #R07172) and 10 mL of TSB (Remel lot #R07226) were each inoculated with 0.5 mL of the sample and were labeled with the study number and day.

The TSB samples were incubated at 25°C, and thioglycollate broth samples were incubated at 35°C, for 14 days, then inspected for growth. The results were reported to the principal investigator for recording in the study file.

We inculcated vials of growth media with the listed organisms, to be used as positive controls. We also left unopened vials of the media for the duration of the study to verify they were not contaminated, to be used as negative controls. These positive and negative controls served to verify growth potential of the culture medium after incubation. The positive controls were tested for Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans yeast, and Aspergillus species, to validate the growth of each organism within the TSB and the thioglycollate broth.

Although the vials were used for a maximum of 7 days, based on previous studies demonstrating that the CSTD maintained sterility for 168 hours, the vials were held for an additional week, to validate the day 8 results and potentially stimulate studies of a longer beyond-use date.

Results

A total of 50 single-dose vials, with 18 different drugs to which CSTD adaptors had been attached, were tested in the TSB and the thioglycollate broth media on day 8 after initial entry. Overall, 49 vials were tested in the TSB and the thioglycollate broth on day 15, after the 14-day incubation period, with no growth detected in all but 1 drug, as shown in Table 2 (available at www.JHOPonline.com).

The only positive sample was that of carfilzomib, which had a positive result in the TSB and in the thioglycollate broth in the sample collected on day 8. However, this was likely a false-positive result, because during the incubation phase, the TSB and the thioglycollate broth became turbid. Samples of the TSB and the thioglycollate broth were plated directly to blood and chocolate agar in an aerobic and an anaerobic environment, with negative results. A Gram stain of each sample was then performed, to determine if there were any visible microorganisms. The Gram stains were negative. In 1 sample of carfilzomib, the microbiologist noted an instant chemical reaction with both media with the day 15 test. A second carfilzomib sample on day 8 produced the same results. These results were believed to be the result of the short (ie, 24 hours) stability of the opened carfilzomib vials, because the drug is prone to degradation at high and low pH levels, as well as high and low oxidation levels. Subsequently, we eliminated carfilzomib from the list of agents to be considered for extended beyond-use date.

After excluding the 2 carfilzomib samples, 48 single-dose vials were tested on day 8 and on day 15 after initial entry. As shown in Table 2, no additional growth was found in any sample in the TSB or in the thioglycollate broth medium after 14 days of incubation.

Discussion

Our results support the findings of previous studies that the PhaSeal CSTD maintains the sterility of intravenous solutions and allows extension of the beyond-use date of single-use vials up to 15 days. Using this CSTD to extend the beyond-use date also offers the possibility of using the device to maximize the use of drugs, hazardous or nonhazardous, that are in short supply, reducing the need to omit treatment or to switch to alternate therapies when the preferred agent is in short supply.

Our findings also indicate that the sterility of used vials was maintained for up to 15 days after the vials were originally opened. This supports a beyond-use date of at least 7 days, and possibly as long as 15 days, for drugs that are chemically stable for that length of time. The stability of the drugs must also be taken into consideration when considering an extension of the beyond-use date; not all agents are stable for 7 days or longer after opening the vial.

The use of 2 growth media to test used vials, and the submission of blinded samples to the center’s Microbiology Department is a practical procedure for documenting that the sterility of vials with PhaSeal adaptors attached is maintained during routine compounding of parenteral medications.

As noted by Edwards and colleagues, extending the beyond-use date and using vials more than once is not feasible in payment systems that require billing for the whole vial rather than for the actual amount of the drug used. Therefore, changing reimbursement policies to allow billing for partial vials would be fiscally responsible and would also decrease employee exposure to hazardous agents, and reduce the amount of hazardous material that must be properly disposed of.

Limitations

The major limitation of our study is the small sample size. There were several reasons for this. It is common for some patients to receive treatment with similar regimens on the same clinic day, allowing for multiple doses of a drug to be prepared simultaneously. This reduced the overall number of vials used, with a concom-
itant reduction in the number of samples available. In addition, a larger percentage of vials were completely empty, further reducing the number of samples that could be obtained for this study.

The relatively short time of this study, and because only vials actually used for preparation of medications administered to patients were used, were additional contributors to the small sample size.

In addition to reducing the number of vials that were available for study, several drugs for less common malignancies, which were identified as eligible for inclusion, were not dispensed during the study period, further reducing the number of samples available for testing.

Conclusion

Our findings show that the PhaSeal maintains sterility of single-use vials of antineoplastic drugs and monoclonal antibodies for up to at least 7 days, and up to 15 days in an active practice setting. Our findings further support the use of this CSTD to minimize drug waste, reduce the impact of drug shortages on patient care, as well as reduce overall drug expenditures, in addition to the device's original purpose of preventing occupational exposure to hazardous agents.

Acknowledgment

The opinions or assertions contained in this article are the private views of the authors and are not to be construed as official, or reflections of, the views of the US Department of the Army, the US Department of the Navy, or the US Department of Defense.

Author Disclosure Statement

Major Uy holds stocks of Pfizer; Dr. Edwards is on the Speaker's Bureau for Pharmacyclics, Celgene, and Seattle Genetics; Mr. Solimando reported no conflicts of interest.

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