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Second Look at Utilization of a Closed-System Transfer Device (PhaSeal)

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Use of closed-system transfer devices (CSTDs) has become an integral part of the processes associated with preparation of hazardous medications. Traditionally, CSTDs have been used to reduce the amount of exposure to hazardous medications experienced by healthcare workers. However, 1 device in particular, PhaSeal (Carmel Pharma AB, Goteborg, Sweden), has also been proved to prevent contamination and potentially extend the beyond-use date (BUD) of pharmaceuticals otherwise limited by US Pharmacopeia Chapter 797 (USP <797>) sterility limits, which has the potential to decrease waste.[1] Decreasing waste would not only provide significant cost savings for healthcare systems, but also assist with preventing wastage of medications that are in critical short supply.

Healthcare costs in the United States continue to be an area of great concern. Projections indicate that sometime between 2018 and 2020, the healthcare budget in the United States will increase to more than 20% of the gross domestic product. Traditionally, the rate of growth of drug expenditures has exceeded the rate of growth of total healthcare expenditures.[2] In recent years, there has been equilibration between the rate of growth of total healthcare costs and the rate of growth of pharmaceutical costs. The Centers for Medicare & Medicaid Services has projected a 5.2% growth rate in overall healthcare expenditures in 2011. However, clinic-administered antineoplastic agents have seen much higher increases in cost growth. For example, there was a 9.5% increase in costs between 2009 and 2010. As such, there is tremendous potential in this area for significant cost savings.

At the same time that US healthcare costs are a concern, there is also an increased focus on improving quality and safety. To ensure patient safety associated with the use of parenteral medications, USP <797> contains standards for healthcare facilities to use as guidelines when preparing compounded sterile products. Furthermore, USP <797> is

ABSTRACT

Objectives: To assess the ability of the PhaSeal system to maintain product sterility given current US Pharmacopeia Chapter 797 and International Organization for Standardization standards for use.

Study Design: Nonrandomized, multicenter trial with interrupted time series design.

Methods: Aliquots of sterile culture medium were transferred from test vials of sterile culture medium to intravenous (IV) bags of sterile medium over a 7-day time period utilizing the PhaSeal closed-system transfer device. The IV bag test samples were then held under controlled incubation for 14 days, and monitored for evidence of contamination by an independent microbiology laboratory.

Results: The results indicated that at the 168-hour mark, the probability of failure was 0.3%. In other words, at 168 hours one would expect there to be a 99.7% probability that the vial would not be contaminated with bacterial growth if the same procedures were utilized under the same environmental conditions.

Conclusions: Although the use of closed-system transfer devices has traditionally focused on reducing exposure of healthcare workers to hazardous substances, this study further demonstrates the PhaSeal system's utility in extending the beyond-use date (BUD) and therefore reducing waste of viable pharmaceuticals. Extending the BUD results in improvements in the supply chain, beneficial effects on the environment, and significant cost savings for the healthcare system.

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PRACTICAL IMPLICATIONS

PhaSeal, a closed-system transfer device, has been proved to prevent contamination and potentially extend the beyond-use date (BUD) of pharmaceuticals otherwise limited by US Pharmacopeia sterility limits.

- Results of a multicenter trial of the PhaSeal system indicated that at the 168-hour mark, the probability of failure was 0.3%.
- Expansion of the BUD would result in improvements in the supply chain, beneficial effects on the environment, and significant cost savings for the healthcare system.

enforceable by the Food and Drug Administration (FDA) and can be surveyed by The Joint Commission or adopted by state boards of pharmacy. In particular, current USP <797> standards mandate that nonpreserved or single-dose vials must be discarded 1 hour after punctured if the puncture occurred outside of International Organization for Standardization (ISO) 5 air conditions, or after 6 hours if the vial was punctured and retained in an ISO 5 environment.[3] However, it should also be noted that USP does allow for extending the BUD based on studies conducted to demonstrate the validity of the extension. While these standards are aimed at improving patient safety and ensure sterile product integrity, they also increase waste and overall healthcare cost due to the relatively short BUDs imposed.

The currently accepted definition of a CSTD endorsed by the National Institute for Occupational Safety and Health, the American Society of Health-System Pharmacists, and the International Society of Oncology Pharmacy Practitioners is "A mechanically closed system that prevents the entry of contaminants into the system or the escape of drug or drug vapor out of the system."[4-6] Numerous peer-reviewed published studies have demonstrated the ability of the PhaSeal system to meet this definition.[7-9] Additionally, the FDA has recently taken a position on CSTD technology by announcing its intention to establish a new product code, labeling standard, and testing definition for CSTDs. The new standard will provide clarity in the future, as there has been much debate among manufacturers about the validity of products claiming to be a CSTD.

To date, the majority of studies utilizing the PhaSeal system have focused on its ability to protect healthcare workers. In other words, studies have focused on the second part of the CSTD definition—prevention of "the escape of drug or drug vapor out of the system." However, our group recently conducted and published a study that examined the first component of the CSTD definition: the prevention of "the entry of contaminants into the system...." The rationale for our first study was to demonstrate how the use of the PhaSeal system would maintain a closed-system environment that would allow for an expansion of the BUD. By preventing the entry of contaminants into the system and maintaining a sterile environment, PhaSeal could extend the use of these products and help reduce the amount of viable product being discarded. Using a multivariate interrupted time analysis, our results demonstrated a 98.2% probability that the vial contents would be sterile at 168 hours. One limitation of the study was the method of "opening up" the CSTD to perform subcultures. Although this was necessary to identify any contamination, it does not apply to compounded sterile product control issues from a real-life perspective.

Accordingly, we designed a second study to improve on our methodology and eliminate this variable. Intravenous (IV) bags were utilized, and 100% of each of the primary test vial contents was distributed into 5 IV bags of sterile culture medium via the PhaSeal CSTD under study. This procedure eliminated the major variable from our first study that may have contributed to observed contamination. As in our first study, we conducted this study at 4 different centers: the University of Texas, MD Anderson Cancer Center in Houston, Texas; the Swedish American Hospital in Rockford, Illinois; Indiana University Health University Hospital in Indianapolis, Indiana; and The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital in Columbus, Ohio. Three centers used a biological safety cabinet (BSC) and 1 used a compounding aseptic containment isolator as their primary engineering control. For secondary engineering controls, 3 sites had USP-compliant negative-pressure ISO 7 clean rooms, and 1 site had a USP-compliant isolator room (negative pressure with at least 12 air exchanges per hour). All primary and secondary engineering controls were certified to be operating within USP standards. All samples were collected during normal working hours under normal working conditions.

The objectives of this second study were the same as those of the first study.[1] The primary objective was to assess the ability of the PhaSeal system to maintain product sterility given current USP <797> and ISO guidelines for use. The second objective was to determine whether the vials could be used over an extended period of time while maintaining sterility.

Our primary testable hypothesis for this study was identical to that of our previous work. The null hypothesis

was that utilization of the PhaSeal System has no effect on product sterility and does not prevent microbial contamination and growth. The alternative hypothesis was simply that the PhaSeal system does have an effect on product sterility and will prevent microbial contamination and growth.

METHODS

For this study, culture medium was utilized as the "product" being tested. The culture medium was prepared and handled as in the first study by an independent laboratory. Pretesting and posttesting quality assurance was conducted on both the vials and IV bags of culture medium. Quality assurance testing included the use of positive and negative controls. The culture medium was initially quarantined for 14 days and preincubated at the laboratory, and all vials were observed for any overt evidence of contamination. Representative samples were also subjected to microbiologic examination to verify sterility. All product manipulations in the pharmacy were performed in ISO 5 conditions utilizing either a biological safety cabinet or a compounding aseptic containment isolator as the primary engineering control. All primary engineering controls used in the study had evidence of certification to ensure operation within required standards as outlined in USP <797>. All sites also utilized the same cleaning procedures during the study. Control culture medium was retained by the laboratory and kept in a controlled environment for continuous evaluation of any potential contamination. Control growth medium was also inoculated with a known quantity of 4 different known organisms and observed visually and microscopically at 24, 48, 72, 96, and 168 hours to verify the growth potential of the culture medium following preincubation.

The following equipment and supplies were used for this study:

- PhaSeal Protector.
- PhaSeal Injector Luer Lock.
- Infusion Adapter.
- Culture medium vials (Bio-Med QC tryptic soy broth 20 mL, The American Society of Microbiology, USP).
- Culture medium bags (Bio-Med QC tryptic soy broth 100 mL, The American Society of Microbiology, USP).
- Sterile syringes (5 mL).
- Sterile/nonsterile gloves, sanitized periodically.
- Sterile isopropyl alcohol pads (medium).
- Sterile isopropyl alcohol 70% spray bottle.

Procedure

Day 0. Ten each of the PhaSeal Protector, Adapter, and Injector assemblies were placed in the primary engineering control (PEC). Hands were washed and gloves were donned and sanitized prior to work in the PEC. The ISO class 5 work surface and the materials that were introduced into the hood were sanitized with 70% isopropyl alcohol according to USP <797> standards. Consecutively numbered "day 0" bag labels were affixed to the front of selected 100-mL tryptic soy broth (TSB) bags. Matching numbered vial labels were affixed to selected vials. Initially, 10 complete test setups were placed in the PEC. Following the first batch setup, test IV bags, vials, and disposables were placed in the PEC by an assistant to preclude the operator from having to remove his/her hands from the PEC. The operation became somewhat continuous, with the assistant providing a flow of new test materials and removing used bags and vials for storage and shipping to the lab. The operator resanitized his/her gloved hands periodically throughout the sample run. The glove resanitization goal was to perform that operation before each of the 10 sample preparations. The first 100-mL TSB IV bag was hung from the IV bar. The cap was removed from the matching numbered 20-mL TSB vial. The vial septum was sanitized by wiping with alcohol across the top, from the septum across the aluminum rim, in a unidirectional motion 1 time. The alcohol was allowed to dry for at least 10 seconds. The PhaSeal Protector was removed from its wrapper aseptically by only touching the expansion bell or the green cap. The injection port remained sterile. The cap of the PhaSeal Protector was aseptically removed from the bottom side and placed over the injection port of the PhaSeal Protector. The PhaSeal Protector was attached to the vial. The spike port cap of the IV bag was removed, and the port rim was sanitized with an alcohol swab. An Infusion Adapter was aseptically removed from its sterile packaging and inserted into the 100-mL IV bag of TSB. The injector was attached to a 5-mL syringe and then 4 mL of air was drawn up. The cap of the Protector was removed and the syringe-Injector combination was engaged. After air was injected into the vial, the vial was inverted and 4 mL of TSB was withdrawn. The syringe-Injector combination was detached from the vial-Protector combination. The syringe-Injector combination was attached to the port on the Infusion Adapter, which had been attached to the IV

bag. A second Protector was opened, and the sterile cap was attached to the TSB vial to protect its injection port during storage outside of the PEC. The new Protector was discarded. The contents of the syringe were injected into the IV bag. The Injector/syringe assembly was disconnected from the Infusion adapter/IV bag assembly and discarded. Intravenous bag 1 and the Protector-vial combination were placed in a plastic zipper bag to protect them if they were stored outside of an ISO-5 environment. The procedure was repeated for the remaining day 0 preparations (83 total). The entire procedure from day 0 was repeated at days 1 (24 hours), 2 (48 hours), 3 (72 hours), and 7 (168 hours).

Microbiologic Protocol

Experimental Design Overview and Microbiologic Testing. The study test medium used was TSB in 100-mL IV bags and 20-mL vials as used in the Bio-Med QC, LLC, media-fill aseptic technique test kits. Each participating institution received 83 vials of the medium to be used for the primary test vials that were stored at room temperature between sampling periods. Each primary test vial had a total of five 4-mL aliquots withdrawn from it over the 168-hour study time period, thereby transferring all of the potentially exposed culture medium to the IV bags for sterility testing. Each withdrawal was transferred via the PhaSeal system under test to a separate 100-mL IV bag of TSB using the PhaSeal Infusion Adapter on the bag to provide a completely closed transfer mechanism, unlike the first study, which required the system to be "opened" to procure a subculture sample for sterility testing. Each institution received 415 bags of TSB for this purpose.

Individual 4-mL aliquots withdrawn from the primary test vial and transferred to an identically numbered and dated IV bag totaled 83 per withdrawal test day per institution. The first withdrawal followed the application of the PhaSeal Protector device to the 20-mL vial of TSB. That point in time was identified as hour 0; subsequent withdrawals and transfers to the next sets of bags occurred at 24 hours, 48 hours, 72 hours, and 168 hours. In all, 4 participating institutions each completed 415 total transfers, 83 per sampling session over the 7-day study period.

The IV bags prepared each day in the pharmacy were individually packaged in foil-coated, insulated bubble pouches and boxed for overnight courier delivery to the laboratory for incubation and monitoring under controlled and microbiologically optimized conditions. Upon receipt, IV bag samples were examined initially for visible growth and then held under controlled incubation at 35°C ± 1°C for 14 days. The bags were examined for microbial growth daily for the first 7 days and a minimum of 2 times during the 8th to the 14th day of the incubation period. One IV bag of 1660 total test samples showed visible contamination at 48 hours of incubation. That test medium sample had been drawn and transferred to its IV bag during a 24-hour sampling session. The 0 hour and subsequent IV bags (ie, hours 72, 96, and 168) of the same sample number all tested negative for contamination. The primary vial number 93 was lost or accidentally discarded after the 0-hour withdrawal from it; therefore, no IV bag samples were submitted for testing after hour 0 for sample number 93. Intravenous bag sample number 181 for the 48-hour draw was removed from the data set due to accidental exposure of the medium in the laboratory after 72 hours of incubation without showing any indication of microbial growth.

The on-site test protocol utilizing the PhaSeal system precluded sanitization of septa and connection interfaces other than the septa of the primary test vials and the rims of the IV bags' spike ports, following the removal of their protective caps.

All containers of the culture medium used in the study were initially quarantined for 14 days at room temperature, and tested for growth potential with American Type Culture Collection (ATCC)-defined organisms, per USP requirement. Prior to distribution to the participating institutions, all containers of culture medium, including extra growth study samples, were preincubated at 35°C for an additional 14 days. Following preincubation of the IV bags, including 25 quality care samples for each participating institution, each set of 25 positive control test bags was inoculated with low concentrations of ATCC quality control microorganisms to verify continued growth support potential. The low concentrations of test organisms were prepared through serial dilutions of ATCC licensed product supplied by Microbiologics, Inc. Each set of 25 pretest quality care bags was divided into 5 groups of 5 bags, and each group of 5 bags was inoculated with a different one of the 5 organisms listed in **Table 1**. Final concentrations of the quality control organisms prepared through serial dilutions were approximately 0.5 colony forming units (CFUs) per mL. Actual concentrations are tabulated below. All pretest growth study samples were visibly positive within 48 hours of incubation at 35°C.

Microbial growth potential of the medium in the IV bags returned to the laboratory from the test sites was also verified by inoculating 25 bags from each participating institution with low concentrations of ATCC quality control organisms. Table 1 defines the organisms used

Table 1. **Description of Quality Control Microorganisms**

Quality Control Organism Name	ATCC ID	ATCC Lot	Final Concentration (CFU/mL)
Aspergillus brasiliensis (niger)	16404	392392	0.46
Bacillus subtilis subsp spizizenii	6633	486-112-1	0.53
Candida albicans	10231	443-111-2	0.51
Pseudomonas aeruginosa	15442	693474	0.48
Staphylococcus aureus	6538P	827-100-2	0.57

ATTC indicates American Type Culture Collection; CFU, colony-forming unit.

and indicates the final average concentration of test organisms in the 100-mL IV bags inoculated for quality assurance testing in this study. A computerized random-number generation system was utilized to identify 100 IV bags (6%) from the 1660 total to be inoculated with the ATCC quality control microorganisms following their use and extended incubation. One bag was selected from each daily preparation set of 83 bags for each of the 5 quality control organisms. The test organisms were reconstituted, serially diluted, and inoculated into their respective IV bags within 30 minutes of rehydration to provide a final concentration per bag of approximately 0.5 CFU per mL. All posttest growth study samples were visibly positive within 48 hours of incubation at 35°C.

Statistical Analysis

The analytic plan of this study was designed to answer 2 primary questions and was identical to the plan of the first study. The first question is, given the parameters of the study, would the CSTD maintain the sterility of the product such that the proportion of samples collected would have a proportion of failures (confirmed bacterial growth) no greater than the proportion of failures due to chance? Second, if sterility can be maintained, how long is it possible to keep the vial in use?

In this follow-up study, we benefited greatly from the prior work in that we had a more precise estimate of the actual proportion of failures. The failure rate in the first study was 1.8% of the tested samples. Therefore, we were able to design the sampling plan around an estimated null proportion of 2% rather than the 5% estimate we used previously. The sampling plan was then implemented to be able to answer the primary question with a 99% (± 3%) confidence level. Originally, the sample design was powered at 0.80. However, the final sample size (n = 331) yielded a post hoc power of 0.921. The increase in power despite the lower-than-designed sample size was due to the rather large effect size observed from the testing.

Results of the microbiologic analysis provided the answer to the first question. Although a total of 1700 samples were tested, the original sample (n = 331) provided the denominator for the test. The resulting failure rate of 0.3% (1 failure out of 331 samples) (99% confidence interval 0.0%-1.0%; $P < .001$) demonstrated that the observed failure rate was significantly different from the hypothesized rate of 2%. Therefore, we can be highly confident that the CSTD system was capable of maintaining sterility in a controlled environment. Utilizing the information gained from the microbiologic testing, we ran a secondary analysis of the data based on time to failure. In this case, a Kaplan-Meier[10,11] univariate survival analysis was run using the PROC LIFETEST procedure available in SAS 9.2 (SAS Institute Inc, Cary, North Carolina). Since the test procedures did not lend themselves to exact timing of the actual moment that the bacterial contamination occurred (nor is that a realistic possibility), the same algorithm described in our first study was applied to determine the cutoff time point for the Kaplan-Meier test (see reference 1).

The results indicated that at the 168-hour mark, there was a probability of failure of 0.3%. In other words, at 168 hours one would expect there to be a 99.7% probability that the vial would not be contaminated with bacterial growth if the same procedures were utilized under the same environmental conditions. The results are summarized in **Table 2** and the **Figure**.

DISCUSSION

Similar to our conclusions from the first study, we found that the PhaSeal system was able to prevent the entry of contaminants into the vials and did maintain a sterile environment. Using IV bags of culture medium allowed for direct introduction of the total contents of the primary vials into the final containers via a closed system. This step eliminated external variables associated with the previous subculture process that were sources of potential contamination. Because vials were used in the first study, it was necessary to remove medium from the vials for subculturing to avoid the potential for false-negative sterility test results. That process in turn created what we thought were some false-positive sterility test results

Table 2. Life Table Estimates of Survival[a]

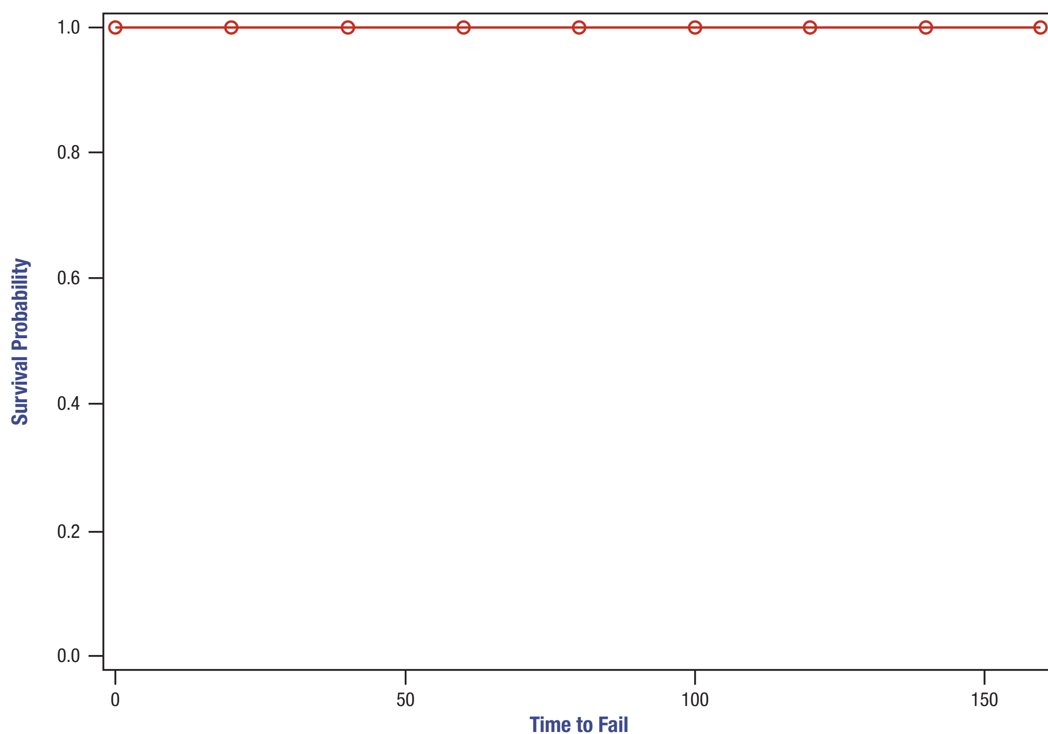
Time Interval (Lower), h	Time Interval (Upper), h	Failure	Sample Remaining	Probability of Survival	Probability of Failure	SE of Survival
0	20	0	331	1.0000	0.00000	–
20	40	1	330	1.0000	0.00000	–
40	60	0	330	0.9970	0.00302	0.00015
60	80	0	330	0.9970	0.00302	0.00015
80	100	0	330	0.9970	0.00302	0.00015
100	120	0	330	0.9970	0.00302	0.00015
120	140	0	330	0.9970	0.00302	0.00015
140	160	0	330	0.9970	0.00302	0.00015
160	180	0	165[a]	0.9970	0.00302	0.00015

SE indicates standard error.
[a]In this case, the nonfailures were considered to be censored. In other words, the vials lasted up to the 168-hour mark. We did not know what happened after that. Therefore, SAS took the remaining sample size and cut it in half to make the final estimation for those who were censored.

by exposing the culture medium to the environment outside of the CSTD under test. Repeated testing of the culture medium for continued growth support potential indicated that the possibility of false-negative results had been eliminated, which further supports the results. Our second study also corroborated the time extension analysis from our first study. In our second study there was a 99.7% probability of vial sterility at the 168-hour mark.

The standards set forth in USP <797> were established to provide guidelines to minimize the potential for contamination of compounded sterile products. USP <797> also allows for extending the BUD, provided objective data exist to support the extension. As a result, healthcare institutions can maximize cost savings by minimizing waste without compromising quality as set forth in USP <797>. The results of our studies have demonstrated that the use of the PhaSeal CSTD on single-use vials does create and maintain a closed environment that prevents the entry of contaminants into the system. This would allow for extending use of the vial beyond the

Figure. Life Table Survival Curve



USP <797> 6-hour standard. Therefore, the PhaSeal CSTD has the potential to provide significant reductions in waste of viable pharmaceuticals. Interestingly, in a study published in *Hospital Pharmacy Europe,* Sanchez-Rubio obtained similar results using PhaSeal and bortezomib.[12] This study demonstrated that the sterility of bortezomib could be maintained for at least 11 days.

It is important to note that the focus of these studies was on extending the BUD based on sterility data. How far the BUD can be extended also depends on the chemical or biologic stability of the product, which must be taken into consideration. Another factor to consider when implementing the drug vial optimization concept is financial and billing regulation compliance. Institutions must evaluate their own specific billing practices before implementing drug vial optimization in their setting. Because the billing of waste is possible through the use of the JW modifier,[13] it is incumbent upon pharmacy managers to discuss and coordinate implementation of the drug vial optimization concept with their individual hospital finance departments. This discussion is imperative to ensure proper billing methodologies and prevent any unethical or fraudulent billing activities. Quantifying waste and its financial impact to an institution can be significant.

An in-depth audit of waste was conducted at the SwedishAmerican Regional Cancer Center in Rockford, Illinois, in 2010. The center was able to determine that approximately $1.2 million worth of savings would be realized by extending the BUD utilizing the drug vial optimization concept. With annual oncology spending of approximately $12 million, these savings are similar to other reported cost savings resulting from prevention of waste of chemically stable medications.[1,14] Preventing this waste would have a considerable financial impact. Preventing waste has an even more significant impact on patient care given the supply issues for antineoplastic agents that have plagued the United States in recent years. Although antineoplastic agents have been disproportionately impacted by supply issues, non-antineoplastic agents have suffered from supply chain interruptions as well. The concept of drug vial optimization for reducing waste of these low-cost but critical medicines could be used to minimize negative patient outcomes associated with drug shortages. In particular, many of the electrolytes that are available in bulk single-dose vials could be given extended sterility dating using this concept.

Limitations

Limitations of this study should be noted. The PhaSeal protectors were recapped during the study procedures using aseptic technique and sterile caps from other PhaSeal protectors. While this recapping was done to minimize variables in this study, it is not real-life practice and these sterile protector caps are not commercially available. Although we do not believe this recapping contributed to the negative culture results, it should be noted. Additionally, the same or a very limited number of personnel were used at each site to conduct the study, performing the aseptic transfers in the same or a very similar manner each time. However, in real life, operations vary among healthcare practices, with some having dedicated personnel to compound antineoplastic and hazardous agents.

CONCLUSIONS

Although CSTDs have traditionally been used to reduce healthcare workers' exposure to hazardous substances, this study further demonstrates the PhaSeal system's utility in expanding BUDs and therefore reducing waste of viable pharmaceuticals. Extending the BUD results in improvements in the supply chain, beneficial effects on the environment, and significant cost savings for the healthcare system.

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