Utility of the PhaSeal Closed System Drug Transfer Device

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Spending on healthcare in the United States continues to be a major concern. In 2008 the United States spent $2.4 trillion on healthcare, which was 16.2% of the total US gross domestic product (GDP).[1] That figure rose in 2009 to $2.47 trillion, or 17.3% of the GDP. If this trend continues unabated, projections are that spending will hit $4.4 trillion and top 20% of the GDP by 2018.[2] This continued rise in spending puts extreme pressure on all facets of the healthcare industry. Patients, their families, providers, payers, hospitals, and the government all feel the stress. Clearly, this situation is not sustainable and everyone must work to reduce healthcare costs.

In organized healthcare settings, one of the fastest-growing expense lines is prescription drugs. Drugs routinely consume 10% to 12% of total hospital expenditures, and in some specialty hospitals such as cancer hospitals, that amount is closer to 40% to 50%.[3] With an average cost of $800 million to bring a new drug to market, advances in treatment options come with a significant price tag.[4] Many of the newer drugs are large-molecule monoclonal antibodies. These drugs typically are parenteral medications that come in single-use nonpreserved vials. Current United States Pharmacopeia (USP) Chapter 797 standards mandate that nonpreserved or single-use drugs must be discarded 1 hour after opening if that opening occurred outside of International Organization for Standardization (ISO) 5 air conditions, or after 6 hours if the vial was opened in ISO 5 air conditions and the drug remained in those conditions for the entire time.[5] This USP standard was enacted to provide additional patient protection by minimizing the impact of any microbial contamination of these products that could result in patient harm. Even though these drugs are chemically stable, if unused amounts are present after the stated USP standard

ABSTRACT

Objective: To assess the ability of the PhaSeal closed system drug transfer device to prevent the contamination of parenteral drug products, thereby allowing extended beyond use dating, which could significantly reduce waste and cost of these products.

Study Design: Nonrandomized trial with interrupted time series design.

Methods: The PhaSeal closed system drug transfer device was applied to vials containing sterile culture media. The vials were entered using the PhaSeal system and samples were removed at 24, 48, 72, 96, and 168 hours. Samples were tested by an independent microbiology laboratory for evidence of contamination.

Results: A total of 1328 syringes were produced at 4 different institutions. Visual, microscopic, and microbiologic subculture analyses were performed. A failure rate of 1.8% was observed, which was not greater than expected and supported our alternate hypothesis at the 99% confidence level that the PhaSeal system is capable of maintaining sterility in a controlled environment. Secondary analysis of the data was conducted based on time to failure. The analysis indicated that at the 168-hour mark there is a 98.2% probability that the vials will not be contaminated.

Conclusion: Results of this study show that the PhaSeal closed system drug transfer device does work to provide a mechanical barrier to the entry of contaminants into sterile solutions. The study demonstrates that solutions could be expected to remain sterile for up to 168 hours.

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PRACTICAL IMPLICATIONS

The PhaSeal closed system drug transfer device was applied to vials containing sterile culture media, and samples were removed for testing at 24, 48, 72, 96, and 168 hours.

- The PhaSeal device does work to provide a mechanical barrier to the entry of contaminants into sterile solutions.
- At the 168-hour mark, there was a 98.2% probability that the vials were not contaminated.

times, they must be discarded. This means that across the country significant amounts of high-cost drugs are being thrown away every year. In an audit of one of the oncology infusion clinics at Indiana University Health, the annual drug acquisition cost was approximately $15.5 million and it was estimated that more than $1 million in viable drug product was discarded due to the USP 797 standard.

If a mechanism could be established to ensure sterility of these drugs so that all of the product that was chemically stable could be utilized with little to no waste and no risk to the patient, then a significant amount of drug waste could be eliminated. As a result, the associated cost would be significantly lower.

In the last several years there has been growing interest in the use of closed system drug transfer devices (CSTDs) as a mechanism to protect healthcare workers from exposure to hazardous medications. The National Institute for Occupational Safety and Health (NIOSH), the American Society of Health-System Pharmacists, and the International Society of Oncology Pharmacy Practitioners (ISOPP) have all adopted a standard definition of a CSTD.[6-8] According to these organizations, a CSTD is a device that "mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system."[6] ISOPP summarized this definition as a system that is essentially leakproof and airtight.[8] Numerous studies have demonstrated the ability of the PhaSeal system by Carmel Pharma to meet this definition.[9-11] However, to date the majority of these studies have focused on the ability of the PhaSeal system to prevent the escape of drug or drug vapor from the system.

Recently De Prijck and colleagues studied the ability of different systems, including PhaSeal, to prevent microbial contamination.[12] In their study they inoculated the stoppers on vials with microbial contaminants and then utilized different mechanisms to enter the vials. They measured the amount of contamination present in the vials and concluded that the PhaSeal system did the best job of preventing transfer of contamination from the external vial stopper into the vial.

We wanted to build on the De Prijck et al study and consider the impact that a CSTD like PhaSeal could have on the ability to prevent contamination under normal working conditions. Clearly the De Prijck et al study created extreme conditions with the inoculation of the vial stoppers prior to entry. We believe that the PhaSeal system, properly applied in ISO 5 conditions, creates a mechanically closed system and the entry into PhaSeal via the double membrane also remains mechanically closed, essentially creating a scenario that mimics the sterility conditions present in an unopened vial. If this is indeed the case, then we should be able to use the chemical stability date to determine product expiration rather than the USP standard of 6 hours for products without a preservative that were accessed under ISO 5 conditions.

CLOSED SYSTEM TRANSFER DEVICE DESCRIPTION

The PhaSeal CSTD uses an in-built pressure equalization technique. The vial adapter, called a Protector, uses an expansion chamber that ensures that over-pressurization does not occur during drug preparation. The Protector attaches to the vial and penetrates the stopper with 2 cannulas. One cannula allows for the entry of the syringe needle, and the second allows for air to pass to the expansion chamber. An amount of air equal to the amount of medication must be added to the vial, and the excess air and hazardous medication vapors and particles travel through the cannula into the sealed expansion chamber. This effectively prevents aerosol and vapor leakage from the vial.

PhaSeal also uses a double membrane system to ensure leak-free transfer of drugs. A specially designed needle called an Injector is attached to a standard Luer lock connection syringe and used to access the vial via the Protector. The Injector contains an 18-gauge needle in a sealed chamber behind a membrane. The Protector has a similar membrane at the access point. When accessing the vial, the Injector and Protector are assembled, and the 2 membranes are pressed against each other, creating a seal. The needle from the Injector passes through the dual membrane and into the vial. When removed from the vial, the needle passes back through both membranes, leaving the connection dry when disassembled. In this process, the hazardous drug does not come into contact with the atmosphere and all connections remain dry with no leakage occurring.

The NIOSH clarification also states that the intended function of a CSTD is to maintain sterility of the product.[6] Therefore, a CSTD should not only protect the user from exposure to the hazardous medication, but also maintain the sterility of the product in the vial. If this is true, in theory a single-dose vial may be used with a CSTD for multiple uses without compromising sterility and integrity of the product.

STUDY DESIGN

We designed a multicenter study to simulate a variety of working conditions and equipment in different organizations. Testing was conducted at MD Anderson in Houston, Texas; SwedishAmerican in Rockford, Illinois; Indiana University Medical Center in Indianapolis, Indiana; and the James Cancer Hospital at the Ohio State University in Columbus, Ohio. All organizations followed current USP 797 standards in all facets of the study. SwedishAmerican utilized a compounding aseptic isolator to create their ISO 5 working conditions, whereas the other study sites used Class II Type 2 biological safety cabinets. Testing was conducted by trained intravenous pharmacy technicians during normal working hours and in normal working conditions. All microbiological testing and evaluation were conducted by an independent microbiologist.

The objective of the study was to assess PhaSeal's ability to maintain product sterility over extended periods of time. The *null hypothesis* was that use of the PhaSeal System has no effect on product sterility and does not prevent microbial contamination and growth. The *alternative hypothesis* was that use of the PhaSeal System creates a system closed to microbial contamination and ensures product sterility. For this study, culture medium was utilized as the "product" being tested. The culture medium, which was prepared by an independent laboratory, was initially quarantined for 14 days and preincubated at the laboratory. 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 biological safety cabinets or compounding aseptic isolators 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. On day 7, the controls were sent to the pathology laboratory for analysis. Positive controls were also prepared by the pathology laboratory and tested for growth potential.

The following equipment and supplies were utilized for the study:

- PhaSeal Assembly Fixture
- PhaSeal Protector (P21)
- PhaSeal Injector Luer Lock (N35)
- Culture medium vials (Bio-Med QC tryptic soy broth 10 mL, The American Society of Microbiology USP)
- Culture growth plates
- Sterile syringes (5 mL)
- Sterile syringes (20 mL)
- Sterile gloves
- Sterile isopropyl alcohol pads (medium)
- Sterile isopropyl alcohol spray bottle.

METHODS

On day 1 the PhaSeal assembly fixture was placed in the primary engineering control (PEC) and cleaned with 70% sterile isopropyl alcohol. The work surfaces in the PEC were cleaned with sterile isopropyl alcohol according to USP 797 practice standards. All culture medium vials were labeled with site and sequence numbers for identification. Hands were washed and sterile gloves utilized prior to work in the PEC. Within the PEC, the P21 PhaSeal Protector was removed from the packaging and the protective cap removed. The P21 was placed into the top of the assembly fixture. The cap on the culture medium vial was removed, exposing the rubber stopper, which was cleaned by wiping an alcohol pad across the top of the septum in a unidirectional motion 3 times. The alcohol was allowed to dry for at least 10 seconds. The culture medium vial was placed onto the base of the assembly fixture, and downward force was applied on the fixture handle to attach the P21 to the culture medium vial to create a Protector Assembly. This process was completed for 83 vials. All vials were subsequently removed from the PEC and stored upright at room temperature in the pharmacy.

Twenty-four hours later, the first samples of the culture medium were withdrawn from the vials. The PEC

was again cleaned with 70% sterile isopropyl alcohol, including the assembly fixture. Hand washing and sterile gloves were utilized in accordance with USP 797 standards. The vials were returned to the PEC, and the membrane of the P21 was cleaned with 70% sterile isopropyl alcohol. Contact was made with the membrane for 3 to 5 seconds, and the alcohol was allowed to dry for 1 minute. Within the PEC, the N35 Injectors and 5-mL syringes were removed from their packaging. Working within the PEC, 2 to 3 mL of air was aspirated into the syringe and the syringe was Luer locked to the N35 Injector, creating a Syringe Assembly. The Syringe Assembly and Protector Assembly were engaged and activated utilizing the push-turn-push technique required for proper use of these PhaSeal components. The culture medium vial was kept in an upright position and air was pushed into the vial. The system was then inverted and 2 mL of the culture medium was removed into the Syringe Assembly. The Syringe Assembly was disengaged from the Protector Assembly using the prescribed pull-turn-pull motion. The N35 Injector was checked to ensure that it was securely Luer locked to the syringe and the syringe was labeled for identification. This process was completed for all vials. Syringes were then sent to the microbiology laboratory for testing, utilizing a designated overnight carrier. Protector Assemblies were again removed from the PEC and stored in an upright position at room temperature in the pharmacy. This process was then repeated at each site at 48, 72, 96 (1 site only), and 168 hours.

MICROBIOLOGY PROTOCOL

Preuse quality assurance was conducted. All newly prepared lots of culture medium were quarantined for 14 days for sterility per USP and tested for growth potential. Prior to release of the test vials for distribution to the various test sites, the vials were preincubated at 37°C for 48 hours. Following preincubation, 33 vials were selected at random and delivered to the Indiana University Health Pathology Laboratory for independent growth studies using diluted inoculate of American Type Culture Collection stock strains for *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Aspergillus fumigatus*.

Testing and quality assurance of the samples were done at the Bio-Med QC facilities in Indianapolis, Indiana. Samples were received at Bio-Med within 24 hours of sampling at the test sites. Once received, the samples were placed under controlled incubation for 14 days per USP 797. Samples were examined at 24 hours, 48 hours, 72 hours, 96 hours, and 168 hours along with positive controls (*B subtilis*) and negative controls. All suspected growth in samples and controls was verified microscopically. Since it is generally accepted that it requires an approximate concentration of 10^6 organisms per milliliter to produce a result that is sufficiently visible, relying solely on visual or microscopic examination for verification of sterility is not ideal. To attain further specificity, an additional subculture was performed on all the samples. The Injector was removed from each of the Injector Assemblies under ISO 5 conditions, and 3 drops of the test medium from each syringe were inoculated onto preincubated culture plates in a specific section on each plate. The plates were labeled with the inoculated section so the plate could serve as its own control for any additional growth. It was recognized that by adding the subculture process, we were opening up the closed system and introducing additional variables or points of possible contamination, including the plates themselves.

RESULTS

A total of 1328 syringes were provided by the test sites. Control samples submitted to the Indiana University Pathology laboratory and tested for viability with *B subtilis, P aeruginosa, S aureus,* and *A fumigatus* were all positive for growth, confirming the growth support potential of the growth media and its ability to demonstrate growth from small inocula (approximately 10^2 colony-forming units [CFU] per milliliter). Positive control samples observed at Bio-Med QC that were inoculated with *B subtilis* and incubated with the test samples all demonstrated visual evidence of contamination. Negative control samples incubated at Bio-Med QC with the test samples all were negative for any visual or microscopic evidence of contamination. Of the 1328 test syringes, 1 showed potential evidence of contamination visually.

The subculture process produced 17 plates out of 1328 with confirmed contamination appearing as single colonies per plate, suggesting they were each formed from single CFUs. Of the 17 positive plates, 11 had growth outside the test area, indicating contamination in the plate itself as supplied from the manufacturer or introduced during the plating process. Six plates had a single colony growing in only 1 of the 3 inoculated potential growth sites in the test area, indicating light growth of contamination drawn into the syringe, plate contamination, or contamination introduced during the plating process.

Table. Life Table Estimates of Survival

Time Interval (Lower), h	Time Interval (Upper), h	Failure	Sample Remaining	Probability of Survival	Probability of Failure	SE of Survival
0	20	0	332	1.00000	0.00000	–
20	40	2	330	1.00000	0.00000	–
40	60	2	328	0.99400	0.00602	0.00425
60	80	0	328	0.98800	0.01200	0.00599
80	100	2	326	0.98800	0.01200	0.00599
100	120	0	326	0.98190	0.01810	0.00731
120	140	0	326	0.98190	0.01810	0.00731
140	160	0	326	0.98190	0.01810	0.00731
160	180	0	163[a]	0.98190	0.01810	0.00731

[a]In this case, the nonfailures were looked at as being censored. That is to say, the vials lasted up to the 168-hour mark. We do not know what happened after that. Therefore, SAS cut the remaining sample size in half to make the final estimation for those that were censored.

All test sites had at least 1 potential positive subculture sample. No positive samples were noted from any site at the 24-hour test. Two potentially positive samples were recorded at 48, 72, and 168 hours. No sites had any multiple positive samples from the same vial (eg, if a vial had a positive sample at 48 hours, the subsequent samples at 72, 96, and 168 hours were all negative). The 6 positive plates were all sent to the Indiana University Health Pathology Laboratory for identification of the CFU species. Organisms identified included 4 isolates of coagulase-negative staphylococcus and 2 isolates of bacillus species.

The analytic plan for this study was designed to answer 2 primary questions. First, given the parameters of the study, would the CSTD maintain the sterility of the product such that the proportion of samples collected would have no more failures (confirmed bacterial growth) than could be expected due to chance? Second, if sterility can be maintained, how long is it possible to keep the vial in use? The sampling plan was implemented to answer the primary question at a 99% (±3%) confidence level. Originally, the sample design was powered at 0.80. However, the final sample size (N = 332) yielded a post hoc power of 0.76.

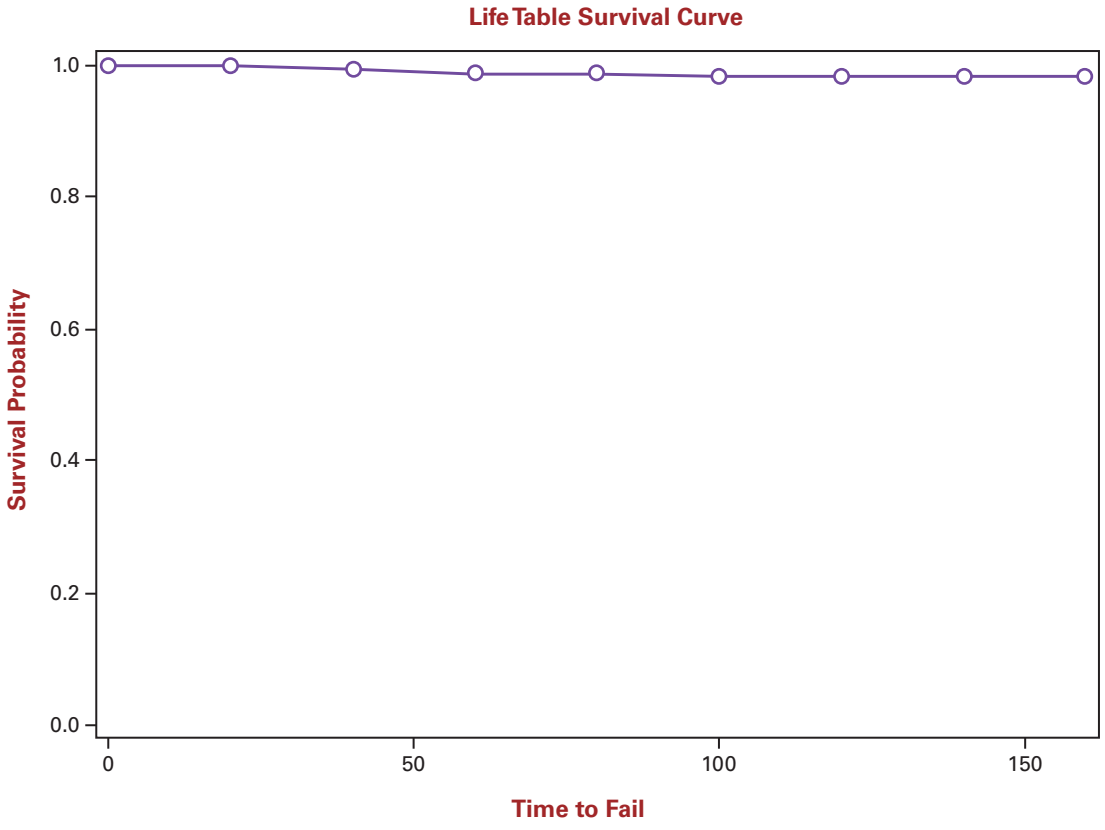
The results of the microbiologic analysis provided the answer to the first question. Although a total of 1328 samples were tested, the original sample (N = 332) provided the denominator for the test. The resulting failure rate of 1.8% (6 failures in 332 samples) (99% confidence interval 0.05%, 3.6%; P <.001) indicated that this rate was not greater than expected. Therefore, the null hypothesis could be rejected in favor of the alternate hypothesis 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 univariate survival analysis was run using the PROC LIFETEST procedure available in SAS version 9.2 (SAS Institute Inc, Cary, NC). 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 algorithm below was used to determine the cutoff time point for the Kaplan-Meier test. Additionally, if there was a failure (either by visual inspection or after plating), the vial was treated as a failure, at which point a time was recorded based on the following:

1. If the sample vial failed at the 24-hour mark, then the failure time = 0 hours.
2. If the sample vial failed at the 48-hour mark, then the failure time = 24 hours.
3. If the sample vial failed at the 72-hour mark, then the failure time = 48 hours.
4. If the sample vial failed at the 96-hour mark, then the failure time = 72 hours.
5. If the sample vial failed at the 168-hour mark, then the failure time = 96 hours.

The results indicated that at the 168-hour mark, there was a probability of failure of 1.81%. In other words, at 168 hours, one would expect there to be a 98.2% probability that the vial would not be contaminated with bacterial growth if the same procedures were used in the same environment type. The results are summarized in the **Table** and the **Figure**.

Figure. Life Table Survival Curve



DISCUSSION

Based on visual and microscopic examination of the 1328 syringes following incubation, 1 syringe exhibited potential evidence of contamination. This was a syringe obtained at the 168-hour test period. Contamination was confirmed as a bacillus species by the Indiana University pathology laboratory. Completing the statistical analysis of these results demonstrated the validity of the alternative hypothesis at the 99% confidence level that use of the PhaSeal system provides a microbiologic barrier and extends sterility of the solution.

All plates used for the subcultures were preincubated to preclude the use of plates that were contaminated in manufacturing or handling prior to use. From the subcultures, 17 plates grew a single colony each. Of these, 11 were outside the control area, indicating that the plates had most likely become contaminated during the plating process. The remaining 6 plates had a single colony in the area where the syringe samples were inoculated, indicating potential contamination of the syringe, contamination of the plate, or contamination introduced during the plating process. New variables were introduced when the initial closed system had to be opened to remove the syringe contents for the subculture process. Contamination could have been introduced at multiple points in that process. No solution showed potential evidence of contamination in more than 1 syringe. This was significant since if the solution had become contaminated during the process, one would reasonably expect that subsequent test samples would also produce subculture growth. The argument may also be made that all subsequent samples might not appear to be positive if very low level contamination was present, because samples could be removed without including the contaminants. However, at 168 hours, the majority of the solution in the vial was removed. In this situation, one would expect that any vial contamination would be captured, but not necessarily that growth would be readily visible; however, subculture growth would be expected from well-colonized vials.

Analyzing these results again supported the alternative hypothesis of PhaSeal preventing microbial growth

at the 99% confidence level. These results indicated that the PhaSeal system, when used in accordance with the aforementioned specifications, had a high degree of precision as an acceptable method to extend the beyond use dating of unpreserved solutions. Additionally, the question of how long the use of a closed system could extend the dating was posed. Based on our study results, extending the dating out to 168 hours could be accomplished with a 98.2% certainty of sterility. Under normal working conditions it should be rare that a vial would require dating this long, but it was our intention to look at the potential worst case scenario in terms of length of time to see if a statistically valid argument could be made.

Our results suggest that the solution in the vials remained sterile throughout the process. However, there still may be a possibility that contaminants were pushed into the vial and only part of the total number of the CFUs introduced with that penetration were removed, and none in subsequent syringe fillings. It is also probable that very low levels of contamination may go undetected due to the growth suppression by the low levels of oxygen present in the airtight syringe.

We are currently conducting a second study with a modified protocol that will allow us to test 100% of the media with more optimal growing conditions. The potential for contamination would appear to be during the transfer of the solution from the vial to the syringe. If contaminants were present on the vial septum surface in low numbers of CFUs, it could be possible to pick up 1 or more of them through the needle puncture and subsequently draw the contamination into the syringe, producing growth in the syringe but not the vial. This also raises the question of the utility of cleaning the vial tops with alcohol pads prior to entry. Although operators start with sterile gloves, as soon as they touch a nonsterile object the gloves are no longer sterile. The alcohol pads are opened with the gloves and the pad itself is then held between the thumb and forefinger of the nonsterile glove surface, which could introduce contamination onto the alcohol pad, which could then be transferred to the vial stopper during the cleaning motion. Typically, waiting for the alcohol to dry before entering the vial does not provide enough time for the alcohol to kill any bacteria that might be present.

We also recognize that the subculture process introduced a significant variable into the study by opening up the closed system. Our second study has been designed with a different process that will test the integrity of the vial and the syringe transfer mechanism without opening up the system, and this study is currently in progress.

CONCLUSION

From the results of this study, it appears that the use of the PhaSeal CSTD does work to provide a mechanical barrier to the entry of contaminants into sterile solutions. The study demonstrates that solutions could be expected to remain sterile for up to 168 hours if the PhaSeal device is applied properly and all additional USP 797 standards are followed. Using PhaSeal for high-cost unpreserved drugs may provide a way to avoid discarding viable drug product because of sterility concerns and help organizations worldwide to reduce waste and drug costs.

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REFERENCES

1. Pear R. Health care spending rises in 2008, but at slower rate. *New York Times.* January 4, 2010.

2. Truffer CJ, Keehan S, Smith S, et al. Health spending projections through 2019: the recession's impact continues. *Health Aff (Millwood).* 2010;29(3):522-529.

3. Wilson AL, American Society for Health-System Pharmacists. *Financial Management for Health-System Pharmacists.* Bethesda, MD: American Society for Health-System Pharmacists; 2009.

4. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ.* 2003;22(2):151-185.

5. US Pharmacopeia. *USP <797> Guidebook to Pharmaceutical Compounding – Sterile Product Preparations.* Rockville, MD: United States Pharmacopeial Convention; 2008. http://www.usp.org/products/797Guidebook/. Accessed January 5, 2011.

6. National Institute for Occupational Safety and Health. *NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.* Atlanta, GA: NIOSH; September 2004. NIOSH publication

2004-165. http://www.cdc.gov/niosh/docs/2004-165/. Accessed January 5, 2011.

7. American Society for Health-System Pharmacists. Continuing education: ASHP guidelines for handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63:1172-1191.

8. International Society of Oncology Pharmacy Practitioners Standards Committee. ISOPP standards of practice: safe handling of cytotoxics. *J Oncol Pharm Pract.* 2007;13(suppl):1-81.

9. Jorgenson J, Spivey S, Au C, et al. Contamination comparison of transfer devices intended for handling hazardous drugs. *Hosp Pharm.* 2008;43(9):723-727.

10. Spivey S, Connor T. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. *Hosp Pharm.* 2003;38(2):135-139.

11. Nygren O, Gustavsson B, Ström L, Eriksson R, Jarneborn L, Friberg A. Exposure to anti-cancer drugs during preparation and administration: investigation of an open and closed system. *J Environ Monit.* 2002;4(5):739-742.

12. De Prijck K, D'Haese E, Vandenbroucke J, Coucke W, Robays H, Nelis HJ. Microbiological challenge of four protective devices for the reconstitution of cytotoxic agents. *Lett Appl Microbiol.* 2008;47(6):543-548. ajpb