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Cost savings realized by use of the PhaSeal® closed-system transfer device for preparation of antineoplastic agents

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Abstract

Purpose: Medication cost is a major factor associated with increasing health care costs in the United States. Expenditures for prescription drugs in 2013 are estimated to be $283.7 billion. Closed system transfer devices are widely used for preparation of hazardous drugs. Reports indicate the Phaseal® closed system transfer device maintains

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sterility in vials for 7 days, suggesting the unused portion of single-use vials could be salvaged. This study was done to determine whether using a closed system transfer device to extend the beyond-use date of single-use vials of antineoplastic medications would result in a measurable cost saving.

Methods: A list of 25 drugs available in single-use vials, with a chemical stability of at least 48 hours, was compiled. Use of these agents was recorded during a 50-day period in April through June 2012. Use from a total of 296 vials of 21 antineoplastic agents was recorded. After allowing for the initial use of each vial, the mean potential percentage of drug waste was calculated to be 57.03%.

Results: Actual savings during the study period was $96,348.70. The pharmacy avoided nearly half of the potential waste and saved a mean of 29% of each vial. The cost-saving during the study period represents a $703,047.67 annual saving; which more than offsets the $106,556.55 the pharmacy spent for the Phaseal® system in 2012.

Conclusion: In addition to being a protective measure to reduce exposure to hazardous agents, use of the Phaseal® system results in a reduction in drug waste, and a noticeable cost saving for antineoplastic agents.

Keywords

Beyond use dating, cost savings, closed system transfer devices, PhaSeal®, single-use vials, USP chapter 797

Introduction

The constantly increasing cost of health care is a major concern to patients, health care providers and insurers.[1] The availability of more expensive, medical technologies and drugs is a significant factor in the increased cost of services.[2] In 2010, expenditures for health care in the United States were nearly $2.6 trillion.[3] In 2013, health spending is projected to grow 3.8%. Expenditures for prescription drugs in 2013 are estimated to increase 2.4%. It is estimated $283.7 billion will be spent on prescription medications in 2013.[4]

The United States Pharmacopeia (USP) chapter 797 mandates that sterile products packaged as single-use vials be used within 6 hours of opening if maintained in an ISO 5 environment or within 1 hour if not kept under ISO 5 conditions. Adherence to this standard causes pharmacies to waste significant amounts of drugs that are expensive or in short supply. The language "...may be used up to 6 hours after initial needle puncture", used in Chapter 797 could be interpreted as allowing more than a single use of an unpreserved vial stored in accordance with the USP requirements.[5] The 6-hour standard is based on microbial growth in various growth media under conditions specified in USP chapter 71 (Sterility Tests). It was not established by direct testing of unpreserved vials in actual or simulated practice environments.[6]

Use of the PhaSeal® CSTD has been proven to reduce exposure to hazardous agents during preparation and administration.[7–15] These devices are recommended by the United States Pharmacopaeia (USP), the American Society of Health-System Pharmacists (ASHP) and the National Institute for Occupational Safety and Health (NIOSH) as a safety measure to prevent occupational exposure to hazardous drugs during compounding and administration.[5,16,17] While not formally recommending use of these devices, the Occupational Safety and Health Administration (OSHA), on its website, has a link to the NIOSH guideline for handling hazardous drugs which does recommend them.[18] Recent studies reported, in addition to minimizing environmental exposure, the Phaseal® CSTD also maintains the sterility of the medication in a vial for at least 7 days.[19–21]

In a comparison of four closed system devices, De Prijck et al.[19] treated parts of the CSTD and the vial stoppers with bacterial inocula, then measured bacterial contamination of the vial following multiple entries into the vial. They reported that without proper disinfection of the vial stopper all the systems showed evidence of contamination. With proper decontamination, the Phaseal® system was the most resistant to microbial contamination of the vial following repeated entry.

McMichael et al.[20] demonstrated that when the Phaseal® system is used within a USP 797-compliant preparation area there is a greater than 98% certainty of maintaining sterility following multiple entries to non-preserved (single-use) vials for up to 168 hours (7 days). In a follow-up study, they reported a 99.7% certainty that sterility was maintained following multiple entries to non-preserved containers to which the Phaseal® device was attached in a USP 797-compliant clean environment.[21] USP Chapter 797 allows compounding personnel to use "appropriate literature sources or direct testing" to extend beyond-use date (BUD) past the limit mentioned in Chapter 797.[5] The data reported by De Prijck's, and McMichael's and Carey's groups meet the Chapter 797 standard of

"appropriate literature sources" as a basis for considering adjustment of the BUD.

In January 2013, the Food and Drug Administration (FDA) issued a Premarket Notification process (501 k) clearance and the ONB (Closed Antineoplastic and Hazardous Drug Reconstitution And Transfer System) product code for the Phaseal® system based on three criteria: no escape of hazardous drug or vapor concentration, no transfer of environmental contaminants, and prevention of microbial ingress.[22,23] This decision by FDA supports the conclusions from De Prijck's, McMichael's and Carey's reports that the Phaseal® system maintains the sterility of vials to which it is attached for up to 168 hours (7 days).

A study of the cost saving from using the Phaseal® system to extend the "beyond use" time of single dose vials estimated a potential cost savings of more than $600,000 in one institution.[24] The objective of our study was to determine if using a CSTD to extend the BUD of single-use vials of antineoplastic medications actually did result in a meaningful cost saving.

Walter Reed National Military Medical Center (WRNMMC) is a 335-bed teaching medical center operated by the US Department of Defense. The Hematology-Oncology Pharmacy Service is a division of the Department of Pharmacy staffed by 3.5 FTE pharmacists, 4 technicians and 1 to 3 Oncology Pharmacy (PGY2) residents. Three of the four pharmacists are certified by the Board of Oncology Pharmacy Specialties as Oncology Pharmacy specialists. Three of the four technicians are Certified pharmacy technicians (CPhT). The oncology pharmacy supports the in-patient and out-patient Adult Medical Oncology, Gynecology Oncology and Pediatric Hematology-Oncology Services, out-patient Urology Service, and Prostate Center. The oncology pharmacy prepares an average of 52 parenteral doses/day (>13,000/year) and fills an average of 17 outpatient prescriptions/day (~4300/year).

Methods

All antineoplastic agents, excluding monoclonal antibodies, used in our oncology pharmacy and packaged in single-use vials were identified. A list of these medications was compiled (Table 1), and the chemical stability of the drug in solution was determined from available literature.[25–35] Medications whose stability was 48 hours or more were included in this study. Medications supplied as injectable solutions were assumed to be stable for 7 days. Medications whose stability following reconstitution is greater than 7 days were listed as stable for 7 days for the purpose of this study.

All parenteral products were prepared in the Hematology-Oncology pharmacy, in ISO 5 conditions using Class II, Type 2 biological safety cabinets (BSC) and USP 797-mandated personal protective equipment in compliance with all requirements of USP Chapter 797.[5] The BSC were certified to ensure operation in compliance with the standards required by USP 797. All Phaseal® devices were attached in accordance with the manufacturer's instructions in the ISO 5 clean room. Prior to this study, the oncology pharmacy discarded all unpreserved vials following the initial use. Even though USP Chapter 797 permits the use of such vials for up to 6 hours after initial use, our practice was to discard them immediately after they were opened.

A data collection form was used (Figure 1) to record the initial dose used, any additional dose(s) prepared, and any drug not used from each vial. For each vial, the actual amount and percent of drug salvaged was recorded. A spreadsheet was created to record the data collected, and calculate the savings realized. These calculations are summarized in Tables 2 and 3.

Between 30 April and 18 June 2012, all partially used vials of medications listed in Table 1 were saved following the initial use. When possible, these partially filled vials were used to prepare subsequent doses of that drug within the 2- to 7-day stability period.

The *Amount Opened* (Table 2) was determined by multiplying the amount of drug in a vial that was used multiple times by the number of vials used (e.g. bortezomib: 24 vials × 3.5 mg/vial = 84 mg). *Initial Use (mg)* was the amount of drug removed the first time a vial was used. Since the amount of drug used varied depending on patient-specific variables, the total amount of drug used from the initial entry into the vials of that drug was calculated by adding the individual dose from each vial. For bortezomib, the *Initial Use* of the 24 vials opened was a total of 41.52 mg. The *Initial Use (%)* was calculated by dividing the *Initial Use (mg)* by the *Amount Opened* (e.g. bortezomib: 41.52 mg ÷ 84 mg × 100 = 49.43%). The amount of *Potential Waste (mg)* was calculated by subtracting the *Initial Use (mg)* from the *Amount Opened* (e.g. bortezomib: 84 mg – 41.52 mg = 42.48 mg). This represents the total amount of drug that would have been discarded if vials were used only once. The *Potential Waste (%)* was calculated by dividing the *Potential Waste (mg)* by the *Amount Opened* (e.g. bortezomib: 42.48 mg ÷ 84 mg × 100 = 50.57%). This represents the overall proportion of the drugs that would have been discarded if vials were used only once.

The Mean of the percentages of *Initial Use* and *Potential Waste* are the average of the *Initial Use (%)* and *Potential Waste (%)* of the individual drugs. A summary of these calculations is in Table 2.

Table 1. Stability of antineoplastic agents packaged in single use vials.

Medication	Stability	Medication	Stability
Aldesleukin	48 hours[25]	Fludarabine	7 days (Liquid)
Alemtuzumab	7 days (Liquid)[26]	Fluorouracil	7 days (Liquid)
Bleomycin	7 days[27]	Gemcitabine	7 days[32]
Bortezomib	7 days[28]	Idarubicin	7 days (Liquid)
Carmustine	48 hours[29]	Ifosfamide	7 days[33]
Clofarabine	7 days (Liquid)	Ipilumumab	7 days (Liquid)
Cyclophosphamide	6 days[30]	Irinotecan	7 days (Liquid)
Cytarabine	7 days (Liquid)	Methotrexate	7 days (Liquid)
Dacarbazine	4 days[31]	Oxaliplatin	7 days (Liquid)
Daunorubicin	7 days (Liquid)	PEGaspargase	7 days (Liquid)
Docetaxel	7 days (Liquid)	Pemetrexed	7 days[34]
Doxorubicin, Liposomal	7 days (Liquid)	Topotecan	7 days[35]
Epirubicin	7 days (Liquid)	Vincristine	7 days (Liquid)
Eribulin	7 days (Liquid)		

Drug: Cyclophosphamide
Contents: 2,000 mg
Date opened: 8 June 2012
Expires: 14 June 2012
Amt used/date: 200 mg/8 June
Amt used/date: 1674 mg/8 June
Amt used/date: 110 mg/9 June
Amt used/date: N/A
Amt Wasted/date: 16 mg/9 June
Wasted: 0.89%
Amt/% saved: 1784 mg/99.1%

Potential waste: 2000 mg (vial size) – 200 mg (initial use) = 1800 mg
Amount salvaged: 1674 mg + 110 mg = 1784 mg
Waste Avoided (%): 1784 mg/1800 mg = 99.1%
Amount wasted (mg): 1800 mg – 1784 mg = 16 mg
Amount wasted (%): 16 mg/1800 mg = 0.89%

Figure 1. Data collection sheet.

Table 3 summarizes the cost savings realized during the study period. The hospital's actual acquisition cost was used for all cost calculations. The *Amount Wasted* is the total amount of drug discarded from all vials of the drug that were used multiple times (e.g. bortezomib: a total of 15.89 mg was discarded from the 24 vials used multiple times). The *Amount Wasted* (percentage) was calculated by dividing the *Amount Wasted* (mg) by the *Amount Used* (e.g. bortezomib: 15.89 mg ÷ 84 mg × 100 = 18.92%). The *Amount Saved (mg)* was calculated by adding the amount of drug used from the individual vials after the initial use (e.g. bortezomib: a total of 26.59 mg was used from the second, or subsequent, use of the 24 vials.) The *Amount Saved (%)* was calculated by dividing the Amount Saved (mg) by the Amount Used (e.g. bortezomib: 26.59 mg × 84 mg × 100 = 31.65%). The mean of the percentages of *Amount Wasted* and *Amount Saved* are

Table 2. Potential drug salvage.

Drug	Amount opened (mg or units)	Initial use (mg or units)	Initial use (%)	Potential waste (mg or units)	Potential waste (%)
Bleomycin	210	103.50	49.29	106.50	50.71
Bortezomib	84	41.52	49.43	42.48	50.57
Cyclophosphamide	36,000	11,403.90	31.68	24,596.10	68.32
Cytarabine	16,200	1269.00	1.20	14,931.00	98.80
Dacarbazine	400	29.80	7.45	370.20	92.55
Docetaxel	1360	691.00	50.81	669.00	49.19
Doxorubicin, liposomal	300	201.80	67.27	98.20	32.73
Erubulin	1	0.75	75.00	0.25	25.00
Fludarabine	100	40.00	60.00	60.00	40.00
Fluorouracil	155,000	62,985.00	40.64	92,015.00	59.36
Gemcitabine	37,600	19,951.50	53.06	17,648.50	46.94
Idarubicin	20	10.40	52.00	9.60	48.00
Ifosfamide	17,000	5250.00	30.88	11,750.00	69.12
Irinotecan	1400	855.20	61.09	544.80	38.91
Methotrexate	4300	967.00	22.49	3333.00	77.51
Mitomycin	10	3.65	36.50	6.35	63.50
Oxaliplatin	1650	1013.5	61.42	636.50	38.58
Pemetrexed	6500	2955.00	45.46	3545.00	54.54
Topotecan	20	4.00	30.00	16.00	80.00
Vincristine	68	24.10	35.44	43.90	64.56
Vinorelbine	250	128.20	51.28	121.80	48.72
Mean			43.45		57.03

the average of the *Amount Wasted (%)* and *Amount Saved (%)*, respectively, of the individual drugs.

Cost savings were calculated by determining the number of vials not used due to reuse of the original vial. For example, if a vial was used three times, the cost saving was calculated as the cost of the two vials that were not used.

Between 30 April and 18 June 2012, all partially used vials of medications listed in Table 1 were saved following the initial use. When possible, these partially filled vials were used to prepare subsequent doses of that drug within the 7-day stability period.

Results

The potential and actual reductions in drug waste and cost saving are listed in Tables 2 and 3. Mean initial use of the vials was 43.45%; leaving a mean of 57.03% of the drug potentially salvageable. Actual waste avoided ranged from 0% (dacarbazine, erubulin) to 93.94% (vincristine). The average overall waste avoidance was 51.35%, which represents an average of 29% per vial. A cost saving of $96,348.70 was realized during the study period. This saving represents a $703,047.67 annual saving; which more than offsets the $106,556.55 the pharmacy spent for the Phaseal® system in 2012.

Discussion

Use of the Phaseal® system to extend the usage of single-dose vials is a simple, readily available method to reduce the waste of medications. The $96,348.70 actual savings identified in this study represents a potential annual saving to our institution of $703,047.67. This is a conservative estimate. At the end of the study period, opened vials that still had drug in them were considered ''expired'', and the residual drug was listed as wasted in our calculations even if the 7-day BUD period had not expired. Partial vials of less frequently used medications (e.g. dacarbazine, eribulin, ipilimumab) could not be salvaged since the interval between doses for a patient exceeded the 7-day stability period; and during the study period an insufficient number of patients received the drug to allow for reuse of the opened vials.

Additionally, several drugs identified as eligible for this study were not actually dispensed during the study

Table 3. Actual cost savings.

Drug	Amount used (mg/units)	Amount wasted (mg or units)	Amount wasted (%)	Amount saved (mg or units)	Amount saved (%)[a]	Cost saving ($)
Bleomycin	210	39.1	18.62	67.4	32.10	383.49
Bortezomib	84	15.89	18.92	26.59	31.65	21,897.92
Cyclophosphamide	36,000	7964.1	22.12	16,632	46.20	6468.25
Cytarabine	16,200	14,665	90.52	266	1.64	20.36
Dacarbazine	400	370.2	92.55	0	0.00	0.00
Docetaxel	1360	57	4.19	612	45.00	17,050.86
Doxorubicin, liposomal	300	21.2	7.07	77	25.67	5508.72
Erubulin	1	0.25	25.00	0	0.00	0.00
Fludarabine	100	30	30.00	10	25.00	84.76
Fluorouracil	155,000	19,961	12.88	72,054	46.49	1070.88
Gemcitabine	37,600	2548.9	6.78	15,099.6	79.80	5399.34
Idarubicin	20	7.8	39.00	1.8	9.00	66.20
Ifosfamide	17,000	6069	35.70	5681	33.42	208.32
Irinotecan	1400	388.8	27.77	156	11.14	50.88
Methotrexate	4300	2721.5	63.29	611.5	14.22	132.84
Mitomycin	10	4	40.00	2.35	23.50	89.14
Oxaliplatin	1650	135.5	8.21	501	30.36	17,951.83
Pemetrexed	6500	305	4.69	2740	42.15	18,799.60
Topotecan	20	10	50.00	6	30.00	620.58
Vincristine	68	2.66	3.91	41.24	60.65	329.68
Vinorelbine	250	34.80	13.92	87	34.80	185.25
Mean			29.29		29.00	
Total						96,348.70

[a]% of overall amount of drug used.

period. Some of these (e.g. aldesleukin, clofarabine, daunorubicin, idarubicin) would have allowed salvage of partially used vials since the daily dosing schedule commonly used for these agents would have allowed saving opened vials for use the next day. Had any of these drugs been used during the study period, the cost saving would have been greater.

As a quality control measure, upon implementation of retaining unpreserved vials for up to 7 days, microbial testing of used vials, and random sampling of opened and unopened vials, will be implemented. All unpreserved vials will be tested when empty, or at the end of 7 days after first use, whichever is earlier. Additionally, at periodic intervals, opened vials will have an aliquot withdrawn and sent for sterility testing. Unopened vials will also be tested periodically as a control measure.

This study was limited to antineoplastic agents compounded in the Hematology-Oncology Pharmacy only. Antineoplastic agents are not the only hazardous agents compounded in many pharmacies. The National Institute for Occupational Safety and Health (NIOSH) lists a number of drugs other than antineoplastic agents in its list of hazardous chemicals.[36] A number are parenteral formulations available in single-use vials (Table 4), which would be amenable to similar cost savings as seen with antineoplastic agents. Use of the Phaseal® system on selected non-hazardous agents could also result in significant cost savings, depending on the cost of the agent, and frequency of use.

A further source of potential savings would be monoclonal antibodies such as bevacizumab, cetuximab, and rituximab. At our institution, the dose of these monoclonal antibodies is rounded to the nearest 100 mg. During our study, this rounding policy resulted in a net cost increase of $924.79, representing an increased annual expenditure of $6750.97 (Table 5).

Had the doses not been rounded and 100 mg vials, plus 200 mg, 400 mg, or 500 mg vials (for cetuximab, bevicizumab, and rituximab, respectively) been used, during the study period, we would have experienced a net cost savings of $10,790.38. This represents a potential annual saving of $78,769.77. This estimate is based

Table 4. Non-antineoplastic agents considered hazardous by National Institute for Occupational Safety and Health (NIOSH).[30]

Drug	Therapeutic classification	American Hospital Formulary System (AHFS) category
Azathioprine	Immunosuppressive	92:44
Chloramphenicol	Antibiotic	8:12
Cidofovir	Antiviral	8:18
Ganciclovir	Nucleoside and nucleotide	8:18.32
Mycophenolate	Immunosuppressive	92:44
Oxytocin	Oxytocic	76:00
Palifermin	Cell stimulant and proliferant	84:16
Pentamidine isethionate	Antiprotozoals, miscellaneous	8:30.92
Plerixafor	Hematopoietic agent	20:16
Valproic acid	Anticonvulsant, miscellaneous	28:12.92
Zidovudine	Antiretroiviral agent	8:18.08
Ziprasidone HCl	Atypical antipsychotic	28:16.08.04
Zoledronic acid	Bone resorption inhibitor	92:24

Table 5. Potential cost savings from not rounding monocolonal antibody doses.

	Bevacizumab	Cetuximab	Rituximab
Dose rounding			
Cost savings ($)	834.81	−1022.25	−737.35
Total actual cost savings ($)		−924.79	
Actual dose (multiple vial sizes)			
Potential Cost Saving ($)	7551.00	1744.45	2097.50
Potential Drug waste (100 mg vial) ($)	138.44	48.84	415.31
Potential Net Cost Saving ($)	7412.57	1695.61	1682.20
Total potential cost savings ($)		10,790.38	
Actual dose (large vial size only)			
Potential Cost Saving ($)	28,487.41	2796.36	39,766.81
Potential Drug waste ($)	217.84	1558.43	1130.21
Potential Net Cost Saving ($)	28,269.57	1237.93	38,636.60
Total potential cost savings ($)		68,144.10	

on the assumption that the actual calculated dose would have been ordered and compounded. Doses would have been prepared using the appropriate number of 200 mg, 400 mg or 500 mg vials, plus the appropriate number of 100 mg vials to achieve the actual dose. Unused portions of the 100 mg vials would be saved for use with the next dose of the agent prepared.

Had only the larger size vials of these drugs been used, and the maximum amount of drug salvaged, our saving during the study period would have been $68,144.10, representing a potential annual saving of $497,451.93. Assuming the same 57.03% of potential waste avoided seen with the cytotoxic agents was realized for these drugs, the savings would have been $38,862.58 and $283,696.83 during the study period and annually, respectively. These estimates are based on the assumption that the actual calculated dose would have been ordered and compounded. Doses would have been prepared using the appropriate number of 200 mg, 400 mg, or 500 mg vials to achieve the actual dose. Unused portions of the vials would be saved for use with the next dose of the agent prepared.

Again, these are conservative estimates. The potential drug waste listed in Table 5 represents the amount of drug that would have remained in a vial at the end of the study period. If, in fact, we were using one of the actual dose policies, those vials might not have been wasted. They would simply have been used on subsequent days after the study was completed. This would have increased our potential annual saving by $356.53 or $11,376.54 annually.

Another potential application of this policy would be for drugs in short supply. At present, 207 drugs are on the ASHP list of drug shortages; some are parenteral agents available as unpreserved solutions or powder for reconstitution.[37] Use of the Phaseal® system to extend the BUD of these vials could allow institutions to conserve scarce resources. Antibiotics, bulk packages, electrolytes, and propofol are examples of products for which institutions could consider using the Phaseal® system to extend the BUD.

An impediment to implementation of this procedure in many institutions is insurance reimbursement policies. There is no incentive for institutions to bill for the actual amount of drug used. Institutions are generally permitted to bill for an entire single-use vial when only part of the vial was used, with various procedures required for documenting the amount of drug wasted.

Using the Phaseal® system to extend the BUD of vials would be a possible method for simplifying billing for some patients. Under certain circumstances, Medicare does allow billing for an entire single use vial when only a fraction of the vial is actually used. This is for drugs covered under Medicare Part B in an outpatient setting. Medicare also has specific coding requirements for the unused portion of the vial and requires fairly complicated documentation for the process, which would seem to discourage billing for the actual amount of drug used.[38] Extending the BUD of single-dose vials would allow institutions to bill each patient's account for the actual amount of drug used without wasting the remainder of the vial. If Medicare, Medicaid, and private insurance billing procedures provided a simple process for coding and billing partially used single-use vials, and provided incentives for institutions to adopt these procedures, the use of a CSTD could extend the life of medications that would otherwise be wasted, reduce overall medication use, enhance the availability of medications in short supply, decrease the amount of hazardous drugs going into the environment, and save money for private insurance payers, the federal government, and health systems.

Conclusion

Significant reductions in drug waste and cost savings were realized through use of the Phaseal® CSTD to extend the BUD of single-dose vials of selected antineoplastic medications. This cost reduction represents a potential annual saving of more than $700,000. If the policy included monoclonal antibodies, an additional annual saving of $44,922.40 to $283,696.84 might have been realized.

If Medicare, Medicaid, and private insurance billing procedures provided a simple, uniform process for billing actual amount of drug administered, and provided an incentive for institutions to adopt such a system, potentially significant reductions in drug expenditures might be realized.

At present, due to current reimbursement policies, such savings may be applicable only to institutions that are not dependent on insurance reimbursement of drug costs, such as government-operated facilities.

Disclosure

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Dual publication

The results/data in this manuscript have not been published elsewhere; nor are they under consideration for publication by another publisher.

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