Economic and Microbiologic Evaluation of Single-Dose Vial Extension for Hazardous Drugs

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Abstract

Purpose: The update of US Pharmacopeia Chapter <797> in 2008 included guidelines stating that single-dose vials (SDVs) opened and maintained in an International Organization for Standardization Class 5 environment can be used for up to 6 hours after initial puncture. A study was conducted to evaluate the cost of discarding vials after 6 hours and to further test sterility of vials beyond this time point, subsequently defined as the beyond-use date (BUD).

Methods: Financial determination of SDV waste included 2 months of retrospective review of all doses prescribed. Additionally, actual waste log data were collected. Active and control vials (prepared using sterilized trypticase soy broth) were recovered, instead of discarded, at the defined 6-hour BUD.

Results: The institution-specific waste of 19 selected SDV medications discarded at 6 hours was calculated at $766,000 annually, and tracking waste logs for these same medications was recorded at $770,000 annually. Microbiologic testing of vial extension beyond 6 hours showed that 11 (1.86%) of 592 samples had one colony-forming unit on one of two plates. Positive plates were negative at subsequent time points, and all positives were single isolates most likely introduced during the plating process.

Conclusion: The cost of discarding vials at 6 hours was significant for hazardous medications in a large academic medical center. On the basis of microbiologic data, vial BUD extension demonstrated a contamination frequency of 1.86%, which likely represented exogenous contamination; vial BUD extension for the tested drugs showed no growth at subsequent time points and could provide an annual cost savings of more than $600,000.

Introduction

The future of health care is a topic of ongoing debate in the US government. Because medication costs constitute a large portion of the budgets of health care organizations, and with continued development of new molecular entities, there is a need for all institutions to evaluate operations to identify opportunities for cost reduction in pharmaceuticals.

Another growing issue gaining significant media attention is the impact of drug shortages. Although these have always occurred, the number and frequency are worse than in previous years.[1] Chemotherapy drug shortages have been most significant with regard to patient impact.[2] Patients have had therapies delayed or have used second-line regimens, because preferred medications were unavailable for use. Methodologies to conserve medications are needed to treat as many patients as safely as possible.

US Pharmacopeia (USP) Chapter <797>, first released in 2004, established federally enforceable practices for preparation of compounded sterile preparations (CSPs). Many in the pharmacy community were not compliant with these regulations when developed. A survey conducted after the release of USP <797> demonstrated that only 35% of respondents had a compliant cleanroom.[3] In addition to organizations planning a new cleanroom, there were other recurring costs that required budgeting, including the personal protective equipment required for daily wear by individuals preparing CSPs and the equipment used for environmental monitoring. Over 75% of hospitals reported increasing their pharmacy budget to accommodate new purchases.

USP <797> has exposure limitations based on air quality set by the International Organization for Standardization (ISO) for medication vials once punctured.[4] Although the original USP <797> differentiated single- (SDVs) from multiple-dose vials (MDVs), it did not specify exposure times or permit the reuse of the vial. The 2008 update included new recommendations for SDV use, stating that SDVs opened and maintained in an ISO Class 5 environment may be used for up to 6 hours after initial puncture.[4] For purposes of this discussion, the exposure limitation is referred to as the beyond-use date (BUD).

Standards used to measure bacterial growth are described in USP Chapter <51> (Antimicrobial Effectiveness Testing). This states that lack of bacterial growth is defined as no more than a $0.5\text{-}\log_{10}$ unit increase compared with the previously measured value.[5] For example, if the properties of a bacteria include a lag time of 6 hours and a population doubling of 30 minutes, then an inoculation of this bacteria in a growth medium of soybean-casein digest would result in a typical microbial growth curve. If 10 colony-forming units (CFUs) per milliliter were introduced into a vial of growth medium at time 0 and incubated appropriately, time 6 hours would demonstrate lack of growth (still 10 CFUs per mL), but time 9 hours would demonstrate microbial growth (640 CFUs per mL). This

is because 640 CFUs per milliliter is greater than a 0.5-log$_{10}$ unit increase from the previously measured value. In this scenario, first penetration of the vial, leading to microorganism entry, would not demonstrate any microbial growth if a 6-hour BUD were adhered to and these assumptions were observed.[6] This standard was used to define growth or no growth in this study. If one CFU was identified during plating, but subsequent sampling showed no CFUs, there was no growth in the vial, suggesting the colony was introduced during the plating process.

The SDV 6-hour BUD was based on a standard microbial growth curve.[7] However, whether systems or different conditions can prevent microbiologic contamination of the contents of a vial or if all medications allow this standard growth has not been evaluated. Additionally, the cost of the remaining medication has not been estimated and could be substantial. This is particularly of note with regard to chemotherapy, in which medication dosing is a factor of weight or body-surface area and usually does not align with manufactured vial sizes. A prior study conducted in Belgium assessed three scenarios for discarding hazardous drug vials: discarding the vial after one CSP, using the vial until the end of the day, and using the vial until chemical expiration date or stability of the drug.[8] Although none of these scenarios were directly applicable to the procedures recommended in USP <797>, the results demonstrated the economics associated with drugs remaining in the vials. Theoretic change in practice from the third to the second scenario resulted in a drug cost increase of 6%, and change from the third to the first scenario resulted in an increase of 13%. If a process could be found supporting the safe extension of the vial BUD without an increased risk to the patient, drug cost savings could be realized.

Closed-system transfer devices (CSTDs) are used to prevent employee exposure to chemotherapy. Studies have demonstrated that settings in which chemotherapy is prepared and administered have documented environmental contamination.[9] The implementation of CSTDs can lead to lower employee uptake and exposure to chemotherapy.[10] De Prijck et al[11] tested the concept of potential for microbiologic ingress in vials during simulated manipulations with contamination artificially placed on the stopper. After the testing of five different devices or methods used in chemotherapy preparation, one process (PhaSeal; Carmel Pharma, Columbus, OH) introduced the lowest amount of microorganisms into the vial and was statistically better than all other processes.[11] It is important to note that contamination was detected in the vial using a CSTD and increased with a larger number of couplings.

At the University of North Carolina (UNC) Hospitals and Clinics, approximately 125 hazardous CSPs are prepared daily, which is associated with a $20 million annual expense. It is imperative to manage and control the costs associated with drug preparation through managing contract, improving drug utilization, and streamlining the steps involved in preparation.

The objectives of this study were first to determine the cost of medications discarded at 6 hours and what savings could be potentially achieved if the BUD were extended to 24, 36, 48, and 72 hours. In addition, the study also sampled and cultured the contents of the vials of both active drugs and controls at 6, 24, 48, and 72 hours and 7 and 14 days to determine the presence of microbiologic contamination and speciation, if found.

Methods

The study design included three phases: a theoretic cost model, projecting annual drug waste calculated from 2 months of dispensing history; using actual waste log data for 6 months to calculate and forecast annual drug waste and compare this with the projected theoretic cost model; and testing microbial contamination of vials by conducting aliquot sampling after antineoplastic CSP preparation of active drug or simulated CSP preparation with trypticase soy broth (TSB).

Theoretic Model

Data from a pharmacy information system were retrieved for March and April 2009. These data included all hazardous CSPs, comprising doses that were prepared with MDVs and SDVs. Hazardous medications were defined based on approved manufacturer package inserts specifying handling requirements and at least one of two qualifications: classified on the National Institute for Occupational Safety and Health list or pharmacology consistent with drugs that may be carcinogenic or mutagenic. Nineteen drugs were selected for analysis based on two criteria: SDV packaging and number and frequency of CSPs. Drugs were excluded if they were MDVs based on 28-day acceptable usage or if <10 CSPs in a 2-month period were prepared. The 2009 acquisition price of each drug was used to determine cost savings with vial extension. Each CSP contained the drug name, dose prescribed, and label print time, which was assumed to be the drug preparation time. Vial sizes were identified that would leave the smallest amount of medication remaining, and the theoretic amount of drug left over (in mg or units) could be determined after each CSP preparation. Knowing the label print time of the following CSP determined if the residual drug could be used in the next CSP. If the label print time were > 6 hours, the remaining drug would be discarded. The investigators used the combination of vials that provided the least amount of residual waste, even if that required more vials for preparation than might be chosen in actual practice. This model was carried through all CSPs made for a 2-month period.

Five additional scenarios were modeled for discarding SDVs and remaining drugs: immediately after one CSP and 24, 36, 48, and 72 hours after initial entry. These times were determined based on the high use of items at this institution and to potentially span a period of Friday to Monday. Respective vial waste was calculated for each time point using previous methodology. Because a 6-hour BUD for SDVs was used, potential cost savings were calculated comparing the 6-hour model with the 24-, 36-, 48-, and 72-hour models.

Actual Model

One practice implemented in the UNC Department of Pharmacy was a daily log of all hazardous vials and CSP waste that was discarded. The theoretic model was evaluated 2 months before this practice. This allowed assessment of vial waste without the use of a theoretic model. At the end of the day, the evening technician would log all remaining medication in SDVs that were beyond 6 hours. Six months of data were collected from June through December 2009 (excluding August because of the opening of new facility), and the same costs from the theoretic model were used.

Microbiologic Phase

Before the microbiologic phase, the investigator was trained in agar plating by a certified medical technologist from the UNC Department of Epidemiology. Ten control vials were plated at each time point during this training. All standard operating procedures were followed in preparing hazardous CSPs. Compounding occurred in an ISO Class 5 biologic safety cabinet within an ISO Class 7 facility.

After the 6-hour BUD, antineoplastic drug vials that had at least 6 mL of drug remaining were sequestered for nonpatient care use instead of being discarded. Six hours was considered time zero for this study, because vial extension would only occur after this time point. Additionally, culturing before compounding was not performed, because it was unknown at that time whether waste would occur. At times 6, 24, 48, and 72 hours and 7 and 14 days, antineoplastic drug preparation was simulated by removing 1 mL of active drug. The simulated preparation occurred under all hazardous medication preparation procedures as required for compliance with USP <797>. In addition, a closed-system transfer device (PhaSeal; Carmel Pharma) was used in each of these simulated preparations. This is the standard process for all chemotherapy preparations. From the 1 mL aliquot, 0.5 mL was transferred to sheep blood agar and 0.5 mL to trypticase soy agar and then incubated for 48 hours in the epidemiology laboratory of the hospital. Each plate was evaluated for microbiologic growth, and if detected, further speciation occurred. Control vials of sterilized TSB (known to allow bacterial growth) were used in addition to active drug. Technicians within the oncology satellite simulated the preparation of CSPs from the control vials, and the investigator collected the remaining vials at 6 hours. All vials were kept at room temperature.

Results

Theoretic Model

The total cost of drugs wasted (using 2009 prices) during the 2-month study period at 6 hours was $127,784, or $766,709 annually. Discarding the vials immediately after use, as opposed to after 6 hours, would result in an increase of $133,054 over 2 months. If regulations allowed BUD extension of SDV use to 24, 36, 48, or 72 hours, the corresponding 2-month total calculated dollars discarded would be $51,195, $36,130, $32,044, and $21,638, respectively. The respective percentages of waste

to overall drug spending would be 2.5%, 1.8%, 1.6%, and 1.1%. The annualized savings based on the overall expenses for these medications at each of these time points would be 3.8%, 4.5%, 4.7%, and 5.3%, respectively. With regard to the projected reduction in overall amount of waste, the percentage of milligrams or units reduced for the modeled time periods was also calculated (Table 1).

Actual Model

Six months of waste log data for these 19 hazardous drugs revealed a calculated cost of $385,444, or annual cost of $770,888. The extrapolated actual cost wasted was similar to the annualized cost of waste for the theoretic model of 19 drugs.

Microbiologic Phase

A total of 101 vials were plated across different time periods: 6, 24, 48, and 72 hours and 7 and 14 days. This included 56 active drug vials and 45 TSB controls. The total number of microbiologic samples was 606. Twelve were discarded because of inappropriate handling, and two were discarded at time 14 days because of no remaining medication. Of the remaining 592 samples, 11 were found to have microbial growth or one CFU on one of two plates. This provided an overall plate contamination rate of 1.86%. Table 2 lists the different time points and the detection of positive samples.

Positive bacterial cultures were speciated; a summary of the organism and number of colonies is found in Table 3. All positive samples were single isolates, and all of the identified organisms are considered environmental contaminants. Zero follow-up samples were positive for either active drug or con-

Table 1. Percent Change of Recovered Drug Associated With Theoretic Waste Model (mg or units)

Drug	0 Hours	6 Hours	24 Hours	36 Hours	48 Hours	72 Hours
Alemtuzumab	23.06	23.06	16.06	7.67	7.67	7.67
Bevacizumab	8.62	6.23	1.18	0.64	0.64	0.31
Bleomycin	34.05	31.60	23.06	23.06	23.06	23.06
Bortezomib	36.89	27.09	11.90	8.07	8.07	8.07
Busulfan	6.94	6.94	6.94	4.67	4.67	4.67
Cyclophosphamide	33.40	9.75	1.95	1.64	1.03	0.10
Cytarabine	62.83	26.84	8.84	5.08	5.08	1.83
Docetaxel	14.21	3.45	0.44	0.44	0.44	0.29
Gemcitabine	12.21	3.00	0.43	0.35	0.17	0.13
Ifosfamide	31.36	28.24	19.04	14.67	12.30	9.79
Infliximab	1.39	1.39	1.23	0.46	0.46	0.15
Irinotecan	10.81	7.38	3.35	3.03	2.70	1.38
Methotrexate (pf)	34.84	16.83	11.56	9.47	8.93	7.56
Oxaliplatin	12.42	6.65	2.46	1.58	1.58	1.28
Pemetrexed	17.13	11.60	10.41	10.41	9.18	5.29
Rituximab	11.70	4.05	0.82	0.51	0.27	0.19
Topotecan	40.63	22.40	10.94	7.80	5.58	3.24
Vincristine	14.58	4.48	1.20	0.99	0.56	0.13
Vinorelbine	11.07	11.07	11.07	10.17	10.17	10.17

Table 2. Positive Samples Per Time Period

Sample	6 Hours	24 Hours	48 Hours	72 Hours	7 Days	14 Days	Total	Overall Rate (%)
Active drug (n = 322)	2	2	1	0	1	0	6	1.86
TSB control (n = 270)	0	0	0	3	1	1	5	1.85
Total (n = 592)	2	2	1	3	2	1	11	1.86

Abbreviation: TSB, trypticase soy broth.

Table 3. Microbiologic Speciation of Positive Samples

Vial No.	Drug	Time Point Positive	No. of Colonies	Organism
15	Oxaliplatin	6 hours	1	*Micrococcus sp*
20	Ifosfamide	6 hours	1	*Bacillus sp*
20	Ifosfamide	48 hours	1	*Moraxella*
21	Cyclophosphamide	24 hours	1	*Bacillus sp*
30	Doxorubicin	24 hours	1	*Bacillus sp*
37	Control vial	72 hours	1	*Bacillus sp*
62	Control vial	7 days	1	*Bacillus sp*
66	Control vial	72 hours	1	*Bacillus sp*
86	Control vial	72 hours	1	*Bacillus sp*
86	Control vial	14 days	1	*Micrococcus sp*
110	Cidofovir	7 days	1	*Micrococcus sp*

trols. In addition, positive samples were found in drugs demonstrated to inhibit microbiologic growth.[12,13]

Discussion

The results demonstrate that adherence to a 6-hour BUD for SDVs has significant economic implications for the drug budget of this hospital. Expanding those costs to similar organizations demonstrates that there could be significant cost savings if the BUD could be safely extended beyond 6 hours. These cost savings were consistent across both the theoretic and actual drug models.

A plate contamination rate of 1.86% was noted for the various tested scenarios. Although this number could be concerning, it is important to critically analyze the reported data and recognize that this is a surrogate end point and not the final CSP.

Each of the detected speciated organisms is associated with exogenous contamination (eg, air, skin). Importantly, the process of transferring the aliquot in the syringe to the agar plate (surrogate end point) required opening of the CSTD and could have lead to introduction of contamination. These steps are not consistent with the usual process of preparing a CSP, in which a closed system is used throughout the whole process. However, the investigators wanted to measure the contamination in the vial, and this was determined to be the best method for this. Further evaluation of the data demonstrated that there were no subsequent positives in any samples. If a growth medium were truly inoculated, one would expect microbial growth over time and the following aliquot to be positive.

One study analyzing the contamination rate of pharmacy CSPs documented a contamination rate of 0.3% when sterile gloves were used with repeated disinfection.[14] As opposed to plating an aliquot on an agar plate, this study used Valiteq Aseptic Technique Validation System (Lab Safety Corporation, Des Moines, IL). A positive sample (failed test) is a cloudy or turbid growth medium. Interpretation of results requires visual examination of the sample, which requires hundreds to thousands of colonies. In our study, all samples were single isolates and would not have been detected as a contaminated CSP using the mentioned methodology.

One study that tested the contamination of the material for wrapping sterile items further supports the idea that contamination could have been introduced through the plating process. From a known sterile item, the investigators detected a plate contamination rate of 1.7%.[15] The assumption is that exposing a microbiologic plate to the atmosphere and swabbing an item could introduce contamination to the plate.

The study conditions included USP <797> recommendations including an ISO Class 5 environment, physical controls (eg, biologic safety cabinets), and employee training in the preparation of CSPs. In addition, a CSTD was used for all preparations (PhaSeal; Carmel Pharma). Until more studies are conducted, the authors do not feel comfortable using BUD extension with a different physical environment or CSTDs. In addition, it is important to note that the vials tested were SDVs and were approved by the US Food and Drug Administration and labeled in that manner, and the patient population receiving those preparations was immunocompromised. Although the cost savings is substantial, and the numerous drug shortages that would somewhat be relieved if all medication in the vial could be used for patient care, USP <797> is the standard by which all CSPs should prepared. However, all guidelines need to be evidence based, and we are aware of no known studies that document the adverse effects of extended BUDs in a controlled environment.

Medicare does allow for billing of the discarded remainder drug. This is only allowed for drugs and biologics covered by Medicare Part B when the patient is located in physician offices, hospital outpatient clinics, and other covered outpatient settings.[16] Challenges do exist when following this regulation, including exclusion of inpatient usage (if medications for both types of patients are prepared in the same location) and the need for proper record keeping for audit purposes. Although allowable, this process still transfers costs back to the federal government, because the discarded medication is not used for patient care.

There are potential limitations to this type of study. When calculating the theoretic drug costs, it was assumed that the medications were compounded at the label print time and that

the vial selection for compounding was selected with the aim of using the least amount of waste. It was also essential that the opened vials were used first. Finally, the waste log data relied on the process of a technician usually inspecting the vial to determine the amount remaining as opposed to drawing the volume up in a syringe.

In conclusion, waste associated with implementation of the USP <797> SDV 6-hour BUD recommendation is substantial. Our theoretic analysis demonstrated that more than $766,000 is being discarded annually, and our waste log reiterates this with an annual cost of $770,888. The evaluation of extending vial life beyond 6 hours was demonstrated with a microbiologic study. A plate contamination rate of 1.86% was detected, with all positive samples having a single isolate. The speciated organisms were all consistent with exogenous contamination, and subsequent sampling of positive vials yielded no growth.

Authors' Disclosures of Potential Conflicts of Interest
Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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