Impact of Robotic Antineoplastic Preparation on Safety, Workflow, and Costs

By Andrew C. Seger, PharmD, William W. Churchill, RPh, MS, Carol A. Keohane, BSN, RN, Caryn D. Belisle, RPh, Stephanie T. Wong, PharmD, Katelyn W. Sylvester, PharmD, Megan A. Chesnick, PharmD, Elisabeth Burdick, MS, Matt F. Wien, BS, Michael C. Cotugno, RPh, David W. Bates, MD, MSc, and Jeffrey M. Rothschild, MD, MPH

Brigham and Women's Hospital; Massachusetts College of Pharmacy and Health Sciences; and Harvard Medical School, Boston, MA

Abstract

Purpose: Antineoplastic preparation presents unique safety concerns and consumes significant pharmacy staff time and costs. Robotic antineoplastic and adjuvant medication compounding may provide incremental safety and efficiency advantages compared with standard pharmacy practices.

Methods: We conducted a direct observation trial in an academic medical center pharmacy to compare the effects of usual/manual antineoplastic and adjuvant drug preparation (baseline period) with robotic preparation (intervention period). The primary outcomes were serious medication errors and staff safety events with the potential for harm of patients and staff, respectively. Secondary outcomes included medication accuracy determined by gravimetric techniques, medication preparation time, and the costs of both ancillary materials used during drug preparation and personnel time.

Results: Among 1,421 and 972 observed medication preparations, we found nine (0.7%) and seven (0.7%) serious medication errors ($P = .8$) and 73 (5.1%) and 28 (2.9%) staff safety events ($P = .007$) in the baseline and intervention periods, respectively. Drugs failed accuracy measurements in 12.5% (23 of 184) and 0.9% (one of 110) of preparations in the baseline and intervention periods, respectively ($P < .001$). Mean drug preparation time increased by 47% when using the robot ($P = .009$). Labor costs were similar in both study periods, although the ancillary material costs decreased by 56% in the intervention period ($P < .001$).

Conclusion: Although robotically prepared antineoplastic and adjuvant medications did not reduce serious medication errors, both staff safety and accuracy of medication preparation were improved significantly. Future studies are necessary to address the overall cost effectiveness of these robotic implementations.

Introduction

Antineoplastic therapy represents a highly beneficial class of medications that must be used with great care because of their toxicity and narrow therapeutic window. Intravenous antineoplastic agents present additional safety challenges.¹⁻⁴ In addition to patient safety concerns, antineoplastic preparation and administration create significant staff risks.⁵⁻⁹

The medication use system includes several stages that are vulnerable to opportunities for potentially harmful medication errors (MEs), such as incorrect drug, dose, concentration, or storage.¹⁰ Recent efforts to improve medication safety have predominantly addressed the ordering, transcription, and administration stages of the system. Technologic solutions have greatly improved medication safety and workflow efficiency during these medication system stages including computerized provider order entry, bar-coded medications, and smart infusion pumps.¹¹

Antineoplastic and adjuvant medication preparation, dispensing, and waste disposal make up a standardized pharmacy process that includes many safety steps.¹² These steps ensure correct matching of the order to the patient and the medication, drug transfer to both intermediate and final delivery containers, and careful disposal of waste. The costs for the process including materials, equipment, and labor are quite high. In addition to the risks to patients, there are risks to staff associated with

exposures to antineoplastics in the form of spills, aerosol exposure, and needle sticks.^{13,14}

Robotic compounding environments offer the potential for safer and more cost-effective antineoplastic and adjuvant medication preparation. However, technologic interventions can also introduce unintended consequences including potential or actual harmful outcomes.¹⁵ Therefore, we undertook a study of the impact of a robotic device that prepares antineoplastics and adjuvant medications on patient and staff safety, unintended consequences, workflow efficiencies, and costs.

Methods

The Brigham and Women's/Dana-Farber Cancer Care Center is a 124-bed inpatient center providing comprehensive oncology care within Brigham and Women's Hospital, a tertiary care 793-bed hospital. In 2009, the Brigham and Women's Hospital pharmacy provided approximately 16,500 antineoplastic and 4,000 adjuvant medication doses.

The primary outcomes were errors with the potential for patient harm (serious MEs) and errors with the potential for staff harm (staff safety events). We also assessed the unintended consequences of robotic use, including mechanical and software failures and the accuracy of prepared drugs, and estimated the labor and ancillary material costs associated with medication

preparation. We did not evaluate the frequency of adverse drug events. Definitions are listed in Table 1.

The study was conducted between May 2009 and April 2011 and was approved by the institutional review board. Consent for voluntary observation was obtained from pharmacy personnel who prepared antineoplastic and adjuvant medications.

Description of Manual Chemotherapy Preparation

The manual process for antineoplastic and adjuvant medication production in the pharmacy during the baseline period is as follows. A physician order in the computerized order entry system is verified by the pharmacist. The pharmacy technician scans the medication and diluent; an additional label instructs the technician as to the volume of medication to add to the diluent bag, and it is brought into the biologic safety cabinet (commonly known as a laminar flow hood) for manufacture. The final product is checked by the pharmacist, who compares the preparation label with all vials used to make the preparation and electronically signs his or her approval in the pharmacy verification system.

Description of the Robotic Intervention

We studied the Health Robotics CytoCare robot (Bolzano, Italy), which was installed in mid 2009. The robot maintains the ISO Class 5 standard for aseptic handling of medications with minimal microbiologic contamination including a negative-pressure environment to protect staff from antineoplastic exposures. The robotically prepared production system is the same as the manual process up to the point of the physical preparation of the products.

The integrity of the microbial and internal gravimetric dose accuracy checking of the robot was validated by outside sources. Before using the robot, test medications were prepared and sent to an outside testing laboratory (Dyanlabs, St Louis, MO). These antineoplastic medications were tested for accuracy, sterility, pyrogenicity, pH level, and concentration before the robot was certified for use. The accuracy testing was done with high-performance liquid chromatography. Recently, the pharmacy department implemented a comprehensive program to test the accuracy of robotically compounded sterile products every 6 months and sterility and pyrogenicity on a weekly basis. The robot also has self-diagnostic software that checks and verifies the balance scale daily before use.

The robotic software organizes the sequence of preparations according to the expected administration time and prompts the technician to scan and load the products for preparation. The products are compounded by the robot through a gravimetric process to precisely weigh the products used to prepare a dose. The final product is considered acceptable by the robot if it falls between $\pm 5\%$ of the expected weight. Products that do not meet this specification are failed by the robot. The pharmacist checks the robot-generated final label detailing how much medication was added to the diluent bag and the final percent variance and verifies this electronically in the robotic software and pharmacy system.

Table 1. Definitions of Outcome Measures

Measure	Definition
Medication error	Any error in the process of ordering, preparing, dispensing, or administering a drug; medication errors identified in this study were only associated with drug preparation
Serious medication error	Medication error with the potential for life-threatening, serious, or significant patient harm
Staff safety event	Potentially hazardous near-miss breach of medication preparation or disposal procedures or policies
Dose variation	Percent difference between the ordered (intended) dose and measured prepared dose
Failed medication preparation	Measured medication preparation that is $> 5\% \pm$ variation from the prescribed dose and does not meet pharmacy quality standards
Mechanical failure event	Failure in the mechanical manipulation of medication vials, syringes, or final administration containers resulting in an incomplete and/or incorrectly prepared product rejected by the robot
Software failure event	Failure in the robotic software system resulting in an incomplete and/or incorrectly prepared product rejected by the robot
Drug preparation time	Observed time taken in the preparation of medications by pharmacy staff including both the pharmacist and pharmacy technician
Ancillary material cost	Cost of materials used to produce an antineoplastic or adjuvant preparation, including hazardous drug protective and containment equipment and additional fluids used to dilute or deliver the active ingredient.
Labor cost	Cost of antineoplastic or adjuvant preparation by pharmacists and technicians based on the amount of time used in preparing medications and hourly salary and fringe benefit rates

Medication and Staff Safety

We directly observed the antineoplastic and adjuvant medication production process as described by Flynn et al,¹⁶ Allan et al,¹⁷ and us¹⁸ in previous observational trials. Nondisguised observations were conducted by trained pharmacist observers using a tablet computer with a Microsoft Access database for time-motion capture.^{19,20} Inter-rater reliability testing was conducted among the pharmacist observers. Potential events recorded by observers were independently reviewed and classified by a physician (J.M.R.) and pharmacist (W.W.C.) experienced in medication safety research. Reviewers were blinded as to the study period of the events.

Events were rated as to the presence of a ME or staff safety event using a five-point Likert scale and the severity of potential harm to patients or staff. Potential severity of patient and staff safety was rated as life-threatening, severe, significant, or little or no harm.²¹ Events rated as little or no harm were not included in the primary outcomes. Events on which the reviewers did not initially come to consensus were adjudicated in person.

Medication Accuracy

Accuracy was determined using specific gravity calculations to compare the actual product dose weight with the ordered dose.²² The specific gravity for each medication and reconstitution fluid was obtained from the manufacturer. A sample of preweighed, prepackaged manufacturing sets was used to standardize and test our process.

For each measured preparation, the variance from the ordered dose was determined. This measurement process was not blinded to the staff because of the pre/post nature of the intervention. The measured preparations were convenience samples chosen on random days not known in advance by the pharmacy staff. Any medication preparation that failed our accuracy measurements was disposed of and was not administered to a patient.

We considered the final product (antineoplastic or adjuvant) preparation to pass the accuracy measurement if the measured weight was within $\pm 5\%$ of the predicted weight and to fail if outside those parameters. The US Pharmacopeia Chapter 795 standard for compounded preparations allows a variance of $\pm 10\%$.²³ We used the tighter variance limits of more than $\pm 5\%$, because they are consistent with our pharmacy standards and the tighter standards of the robot as well. Products with $\pm 5\%$ to 10% variance were rated as insignificant deviations with little or no potential for harm. Products with more than $\pm 10\%$ variance were rated as serious deviations that were potentially harmful.

Workflow of Medication Preparation

A trained research pharmacist conducted the time-motion analysis of the medication preparation workflow at a different time from the safety observations. The production workflow time started during the baseline phase when the pharmacy technician placed the agents and ancillary items in the laminar flow hood and during the intervention phase when the technician placed the products for preparation in the robot. We timed the pharmacy technician completing the drug preparation/manufacture process from that point forward. Technician time when using the robot included loading and unloading the product from the robot. We also included the time required for pharmacist verification.

Costs of Medication Preparation

We calculated the labor costs of the drug preparation time using the time-motion data and the staff hourly wage and fringe rates. The cost of ancillary materials used to make the final products during drug preparation was also calculated. Ancillary materials included syringes, needles, final administration containers, reconstitution fluids, and the components of the closed-system transfer device (PhaSeal; BD, Franklin Lakes, NJ), which included the vial adapter, injection adapter, and infusion adapter.

Unintended Consequences

We also monitored for the presence of unintended consequences. During the observations, we documented mechanical and software failure events that although they had little or no potential for patient or staff harm, did contribute to delays in medication preparation or the need to repeat preparations. The effects of these unintended consequences were also captured in the time-motion analysis of medication production times.

Statistical Analyses

Significance values between the study periods of serious MEs, staff safety events, and medication accuracy were calculated using a two-tailed Fisher's exact test. The Wilcoxon signed-rank test was used to assess variance in the medication doses, workflow, and costs of ancillary goods analyses. The κ statistic was used to determine inter-rater reliability for events.

Results

Safety

A total of 49 and 104 safety observation sessions spanning 87 and 175 hours were conducted in the baseline and intervention periods, respectively. We observed 1,421 and 972 drug preparations (bags and syringes) in the baseline and intervention periods, respectively. We found nine (0.7%) and seven (0.7%) serious MEs ($P = .8$) in the baseline and interventions periods, respectively. No events were judged potentially life threatening, with events nearly evenly split between significant and serious level of harm.

We observed 73 (5.1%) and 28 (2.9%) staff safety events ($P = .007$) in the baseline and intervention periods, respectively (Table 2). All events were judged to be potentially significantly harmful; none were considered serious or life threatening. None of the observed staff safety events resulted in actual harm. Examples of safety events and unintended consequences are summarized in Appendix Table A1 (online only). The inter-rater reliability for event rating was good ($\kappa = 0.51$).

Unintended Consequences

There were 45 events of unintended consequence (4.6%) specifically attributable to the new technology, including 41 mechanical and four software failure events. None of these events resulted in the production of a final product, and they thus were not judged to be serious MEs. These events included 24 cases with no drug injected into the bag or syringe; four cases of drug weight failure rejected by the internal checking system of the robot; three cases of bags, syringes, or needles dropped or cracked before completion; three reconstitution shaker failures; two medication carousel malfunctions; five other mechanical failures; and four software failures preventing drug preparation completion.

Medication Accuracy

We conducted accuracy measurement on 44 days including 184 baseline preparations and 110 intervention robotic preparations (Table 3). In the baseline phase, there were a total of 23 failed preparations (12.5%) and one failed preparation (0.9%) in the intervention period ($P = .002$) using our cutoff point of more than $\pm 5\%$ variance. On secondary analysis using the industry standard of more than $\pm 10\%$ variance, eight preparations (4.3%) failed in the baseline and none failed when robotically prepared.

Workflow of Medication Preparation

We conducted a total of 20 workflow observations including 34 hours observing 281 preparations during the baseline period

Table 2. Types of Errors During Antineoplastic and Adjuvant Medication Preparation

Error Type	Baseline: Manual Preparation		Intervention: Robotic Preparation	
	No.	%	No.	%
Serious medication errors				
Wrong dose and/or final concentration	2	22	6	86
Wrong drug	3	37	0	0
Wrong technique	2	22	0	0
Incomplete seal of medication access port	2	22	0	0
Other	0	0	1	14
Total	9	100	7	100
Staff safety events				
Spill or leak	34	47	23	82
Closed-system transfer device failure	2	2	0	0
Wrong technique	2	2	0	0
Lack of protective equipment	35	48	1	4
Other	0	0	4	14
Total	73	100	28	100

and 18 hours observing 100 preparations in intervention period. The mean preparation times were 7 minutes 24 seconds and 10 minutes 51 seconds in the baseline and intervention periods, respectively ($P = .009$). Although the pharmacy technician's mean drug preparation time increased by 160% (4 minutes 12 seconds *v* 10 minutes 5 seconds), the pharmacist's time decreased by 76% (3 minutes 13 seconds *v* 46 seconds) from the baseline to the intervention period.

Table 3. Accuracy of Prepared Antineoplastic and Adjuvant Medications

Agent	Baseline Period					Intervention Period					P	
	Total Bags No.	Failed Preparation		Percent Dose Variation		Total Bags No.	Failed Preparation		Percent Dose Variation			
		No.	%	Median	Range		No.	%	Median	Range		
		Failed Preparation	Dose Variation									
Antineoplastics												
Busulfan	5	1	20	2.9	7 to −1.5	0	—	—	—	—	NA	NA
Cisplatin	3	0	0	1.8	2.3 to −1.3	3	0	0	2.2	3.6 to −2.0	1	
Cyclophosphamide	48	1	2.1	1.7	5.7 to +1.8	0	—	—	—	—	NA	NA
Cytarabine	50	9	18	2.2	−17.6 to +28.8	26	1	3.8	2.0	−5.8 to +4.1	.15	.16
Etoposide	21	3	14.3	2.7	−12.0 to +1.1	39	0	0	3.8	−1.3 to +5.0	.04	.16
Fludarabine	22	7	31.8	3.8	−51.3 to +1.5	12	0	0	3.1	−5.0 to +0.6	.04	.26
Methotrexate	7	1	14.3	2.6	−8.0 to +2.8	0	—	—	—	—	NA	NA
Mitoxantrone	7	1	14.3	2.7	−7.0 to +0.2	0	—	—	—	—	NA	NA
Total	163	23	14.1	2.1		80	1	1.3	2.9		< .001	.13
Adjuvants												
Leucovorin	0	—	—	—	—	4	0	0	1.8	−2.6 to −1.1	NA	NA
Mesna	21	0	0	2.4	−4.3 to +4.3	26	0	0	1.3	−4.9 to +1.6	1	.05
Total	21	0	0	2.4		30	0	0	1.4	1.4	1	.05
All preparations	184	23	12.5	2.1		110	1	0.9	2.5		< .001	.91

Abbreviation: NA, not applicable.

Costs of Ancillary Materials and Labor

The hourly salary and fringe costs were \$25.44 per hour for pharmacy technicians and \$64.23 per hour for staff pharmacists. The mean total pharmacy labor costs per preparation were \$5.22 and \$5.10 per preparation in the baseline and intervention periods, respectively. The mean costs for ancillary materials per preparation were \$13.36 and \$6.44 in the baseline and intervention periods, respectively ($P < .001$).

Discussion

Robots have been used for several years in pharmacy preparation of predominantly nontoxic medications.²⁴ Our study of a robotic compounding for antineoplastic and adjuvant agents found no overall change in serious MEs, but did find benefits with respect to staff safety and costs. Although we observed no actual events of staff harm during the study, we found a significant reduction in the number of potentially harmful staff safety events, in part because of the containment area of the robot, which is sealed during the compounding process. We found many mechanical or software failure events associated with robotic preparation that were not potentially harmful to patients but did affect workflow and resulted in some wasted medications.

The most impressive finding was the improved accuracy of prepared chemotherapy and adjuvants by robotic compounding, with a reduction in the failure rate from 12.5% to 0.9%. After liberalizing the accuracy standards from $\pm 5\%$ to $\pm 10\%$ variance, we still found impressive improvements in failure rates because of the accuracy of the robot (4.5% to 0%). As a result of these observations, the pharmacy staff underwent reeducation to improve accurate manual preparations under the hood. The

pharmacy also installed the i.v.SOFT gravimetric workflow software (Health Robotics) for manual preparation of antineoplastic and adjuvant medications.

We found that by eliminating the pharmacy technician's handling of open/exposed antineoplastic and adjuvant medications during robotic preparations, we were able to reduce ancillary costs associated with several components of the closed-system transfer device. In both arms of the study, the infusion adapter portion of the closed-system transfer device was still required on the final administration container; the vial and injection adapters used during manual preparation were no longer necessary during robotic preparation. The savings for these components accounted for 60% of the overall cost of the closed-system components, and when annualized for the 16,500 antineoplastic bags/syringes prepared in our hospital in 2009, they would have saved \$115,500 in material costs.

We found no overall change in the pharmacy department labor costs between the study periods; there was a decrease in pharmacist time observed in the intervention period because of the quicker scanning process associated with the robotic software package. The pharmacist could scan the final administration container with all product information displayed on a single screen. This process prevented the pharmacist from having to gather various data, both in computer and written form, to verify all information.

We also found a number of unintended consequences associated with robotic mechanical and software failures. Although the majority of these observations resulted in no medication used before the production was halted, there was wasted medication in a minority of these events. The impact of these unintended consequences on pharmacy costs because of wasted medications could not be determined during our study. Several robotic failures were corrected during and after the latter part of the study with manufacturer updates to software and mechanical features such as improved clamp design and a second robotic arm. Our experience with this early-generation robotic technology is similar to our experience with first-generation smart infusion pumps, where iterative device improvements were made, in part, in response to our findings.²⁵ In that study, we discovered several hardware and software characteristics that have since been improved to reduce pump input errors and risky nursing workflow shortcuts that bypassed the decision support safety benefits of the pump.

Lastly, we cannot make any conclusions about the clinical impact of the enhanced accuracy of robotically prepared medications. It is likely that in the future, technologies will be available to inexpensively and rapidly confirm the concentration and dosage accuracy of a large variety of high-risk prepared intravenous medications such as antineoplastic agents, vasopressors, vasodilators, and narcotics. Such technologies will likely include in-line sensors that can be used in pharmacies, operating rooms, or critical care units.²⁶

Regarding limitations, our study compared only the costs of ancillary items used for medications manually prepared in the baseline period and robotically prepared in the intervention period and did not account for all costs associated with antineo-

plastic and adjuvant preparation. We were unable to measure the impact of the robot on potentially reducing the amount of disposed unused portions of drug vials or increased waste resulting from mechanical failures or any increased waste associated with failed preparations. The cost of this waste cannot be charged to patients, and it adds significant expense to the annual pharmacy budget.²⁷ We did not conduct a comprehensive cost-benefit analysis, which would have included the cost of the robot installation and training pharmacy staff to use the robot. We studied the first-generation model of this particular robot, and during the early study stages, it was programmed to prepare fewer antineoplastics than toward the latter study stages. Although the closed-system transfer device was used in both arms of the study, the robotic process itself does not provide any protection from exposure during the administration of medication beyond the continued use of the infusion adapter by nursing. We did not use wipe, air, or biologic sampling to determine actual exposure to antineoplastic medications in our study. To better understand the amounts of antineoplastic medications that staff are exposed to during preparation of these products, additional studies would need to be performed. Our findings may not be generalizable to other commercially available robotic devices that can prepare antineoplastic and adjuvant medications.

In conclusion, the implementation of a robot to manufacture antineoplastic and adjuvant medications resulted in no change in the rate of serious MEs but did significantly reduce staff safety events when compared with manual preparation. The robot was far more accurate in preparing antineoplastic and adjuvant doses than manual preparation. Unintended mechanical and software failures were introduced by the robot, but these were not considered safety hazards. Additional studies are needed to assess the overall costs and benefits of using this expensive but potentially valuable alternative to manual preparation of antineoplastic and adjuvant medications and the clinical impact of the improved accuracy of preparations.

Accepted for publication on July 18, 2012.

Acknowledgment

Supported by McKesson Automation, Cranberry, PA. Presented in part in poster format at the 45th American Society of Healthcare Pharmacists Midyear Symposium, Anaheim, CA, December 5-9, 2010. We thank Stuart Lipsitz, PhD, Michele Campolieto, PharmD, Kwok Szeto, RPh, and Henry Lam, RPh, for their contributions.

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.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None

Research Funding: Andrew C. Seger, McKesson Automation; Elisabeth Burdick, McKesson Automation; Jeffrey M. Rothschild, McKesson Automation **Expert Testimony:** None **Other Remuneration:** None

Author Contributions

Conception and design: William W. Churchill, Carol A. Keohane, Michael C. Cotugno, David W. Bates, Jeffrey M. Rothschild

Financial support: Jeffrey M. Rothschild

Administrative support: William W. Churchill, Carol A. Keohane, Caryn D. Belisle, Michael C. Cotugno, David W. Bates, Jeffrey M. Rothschild

Provision of study materials or patients: Caryn D. Belisle, Jeffrey M. Rothschild

Collection and assembly of data: Andrew C. Seger, Carol A. Keo-

hane, Stephanie T. Wong, Katelyn W. Sylvester, Megan A. Chesnick, Matt F. Wien, Jeffrey M. Rothschild

Data analysis and interpretation: Andrew C. Seger, William W. Churchill, Carol A. Keohane, Elisabeth Burdick, Matt F. Wien, Jeffrey M. Rothschild

Manuscript writing: All authors

Final approval of manuscript: All authors

Corresponding author: Jeffrey M. Rothschild, MD, MPH, Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, 1620 Tremont St, Boston, MA 02120-1613; e-mail: jrothschild@partners.org.

DOI: 10.1200/JOP.2012.000600; published online ahead of print at jop.ascopubs.org on September 25, 2012.

References

- Jacobson JO, Polovich M, McNiff KK, et al: American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards. *J Clin Oncol* 36:651-658, 2009
- Bonan B, Martelli N, Berhoune M, et al: The application of hazard analysis and critical control points and risk management in preparation of anti-cancer drugs. *Int J Qual Health Care* 21:44-50, 2009
- Institute for Safe Medication Practices: Safe practices in pharmacy sterile compounding areas. <http://www.ismp.org/newsletters/acutecare/articles/20110602.asp>
- Ranchon F, Salles G, Späth HM, et al: Chemotherapeutic errors in hospitalized cancer patients: Attributable damage and extra costs. *BMC Cancer* 11:478, 2011
- Connor TH, DeBord DG, Pretty JR, et al: Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med* 52:1019-1027, 2010
- McDiamid MA, Oliver MS, Roth TS, et al: Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *J Occup Environ Med* 52:1028-1034, 2010
- Chaffee BW, Armitstead JA, Benjamin BE, et al: Guidelines for the safe handling of hazardous drugs: Consensus recommendations. *Am J Health Syst Pharm* 67:1545-1546, 2010
- Davis J, McLauchlan R, Connor TH: Exposure to hazardous drugs in Health-care: An issue that will not go away. *J Oncol Pharm Pract* 17:9-13, 2011
- Falck K, Griffin P, Sorsa M, et al: Mutagenicity in urine of nurses handling cytostatic drugs. *Lancet* 313:1250-1251, 1979
- Morimoto T, Gandhi TK, Seger AC, et al: Adverse drug events and medication errors: Detection and classification methods. *Qual Saf Health Care* 13:306-14, 2004
- Bates DW: Preventing medication errors: A summary. *Am J Health Syst Pharm* 64:S3-S9, 2007 (suppl 9)
- ASHP Council on Professional Affairs: ASHP guidelines on preventing medication errors with antineoplastic agents. *Am J Health Syst Pharm* 59:1648-1668, 2002
- Sessink PJ, Bos RP: Drugs hazardous to healthcare workers: Evaluation of methods for monitoring occupational exposure to cytostatic drugs. *Drug Saf* 210:347-359, 1999
- Summerhayes M: The impact of workload changes and staff availability on IV chemotherapy services. *J Oncol Pharm Pract* 9:123-128, 2003
- Harrison MI, Koppel R, Bar-Lev S: Unintended consequences of information technologies in health care: An interactive sociotechnical analysis. *J Am Med Inform Assoc* 14:542-549, 2007
- Flynn EA, Pearson RE, Barker KN: Observational study of accuracy in compounding IV admixtures at 5 hospitals. *Am J Health Syst Pharm* 54:904-912, 1997
- Allan EL, Barker KN: Fundamentals of medication error research. *Am J Hosp Pharm* 47:555-571, 1990
- Rothschild JM, Churchill W, Erickson A, et al: Medication errors recovered by emergency department pharmacists. *Ann Emerg Med* 55:513-521, 2010
- Rothschild JM, Bartel S, Flynn EA, et al: An observational study of outpatient chemotherapy safety. *J Gen Intern Med* 16:215, 2001 (abstr; suppl 1)
- Barker KN, Flynn EA, Pepper GA: Observation method of detecting medication errors. *Am J Health Syst Pharm* 59:2314-2316, 2002
- Bates DW, Cullen DJ, Laird N, et al: Incidence of adverse drug events and potential adverse drug events. *JAMA* 274:29-34, 1995
- Lecordier J, Heluin Y, Plivard C, et al: Safety in the preparation of cytotoxic drugs: How to integrate gravimetric control in the quality assurance policy? *Biomed Pharmacother* 65:17-21, 2010
- Chapter 795: Pharmacy compounding—Physical tests, in United States Pharmacopeia (ed 27), Rockville, MD, United States Pharmacopeial Convention, 2003, p 2348
- Fox BI, Felkey BG: Automated intravenous preparation: Robots for the pharmacy. *Hosp Pharm* 44:255-257, 2009
- Rothschild JM, Keohane CA, Cook EF, et al: A controlled trial of smart infusion pumps to improve medication safety in critically ill patients. *Crit Care Med* 33:533-540, 2005
- S.E.A. Medical Systems: IV check. <http://www.seamedical.com/?pg=products&sl=iv-check>
- Fasola G, Aita M, Marini L, et al: Drug waste minimization and cost-containment in medical oncology. *BMC Health Serv Res* 8:70, 2008

Appendix

Table A1. Case Descriptions of Safety Events and Unintended Consequences

Potential Harm	Case Description
Serious medication error	
Significant	During baseline period, pharmacy technician did not attach required filter to syringe during withdrawal of clofarabine from vial
Significant	During intervention period, a decitabine bag failed because final product was underdose weight failure of 14.7%
Serious	During baseline period, a decitabine preparation was made but not placed in refrigerator in time to preserve potency
Serious	During intervention period, a cytarabine preparation had syringe leak, resulting in final product that was underdose weight failure of 37%
Staff safety event	
Significant	During baseline period, during withdrawal of a busulfan dose, closed-system transfer device was not placed on vial and syringe
Significant	During intervention period, while preparing a cytarabine bag, large spill occurred in robot, resulting in extensive contamination within robotic cabinet
Mechanical failure event	
None	During intervention period, a preparation of fludarabine product failed to be properly admixed in spinning device
Software failure event	
None	During intervention period, preparation of a fludarabine bag failed because of robot freezing, resulting in rebooting and rework to complete preparation