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Independent consultant; The TECHNA Institute; Princess Margaret Cancer Centre; Canadian Association of Provincial Cancer Agencies; University of Toronto; North York General Hospital, Toronto, Ontario; Alberta Health Services, Edmonton, Alberta; CancerCare Manitoba, Winnipeg, Manitoba; and BC Cancer Agency, Vancouver, British Columbia, Canada

Corresponding author: Rachel E. Gilbert, MA; e-mail: rachel@rachelgilbert.ca.

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Intravenous Chemotherapy Compounding Errors in a Follow-Up Pan-Canadian Observational Study

Rachel E. Gilbert, Melissa C. Kozak, Roxanne B. Dobish, Venetia C. Bourrier, Paul M. Koke, Vishal Kukreti, Heather A. Logan, Anthony C. Easty, and Patricia L. Trbovich

QUESTION ASKED: In the context of chemotherapy compounding, what potential human failures exist that may not yet be addressed by practice standards?

SUMMARY ANSWER: Eleven latent errors in chemotherapy compounding were identified, all of which could lead to death or permanent loss of function among patients with cancer. Errors could have occurred during transcription of the prescription, staging of materials, reconstitution and mixing of the drugs, and verification and labeling of the compound mix. Applicable Canadian and international standards and guidelines do not explicitly address many of the potentially error-prone practices observed in this study.

WHAT WE DID: Field observations in four cancer center pharmacies in four Canadian provinces.

WHAT WE FOUND: A significant degree of risk for serious error in manual mixing practice was observed in this Canadian study.

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATIONS:

It is reasonable to assume that the latent errors observed in this study would exist in other regions where manual compounding of intravenous chemotherapy takes place. There is much room for improvement in intravenous compounding. Continued efforts to advance standards, guidelines, technological innovation, and chemical quality testing are needed. This observational study included a small number of sites in only four Canadian provinces. As a result, the opportunity to observe many other latent errors was likely missed. However, in this small sample, light has been shed on practice issues that are not addressed by most current safety mechanisms. Another limitation is that no actual errors were observed, meaning that it was not possible to know how likely they are to occur. However, for such a high-risk activity as chemotherapy compounding, it is essential to anticipate and address issues before they result in patient harm. **JOP**

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Independent consultant; The TECHNA Institute; Princess Margaret Cancer Centre; Canadian Association of Provincial Cancer Agencies; University of Toronto; North York General Hospital, Toronto, Ontario; Alberta Health Services, Edmonton, Alberta; CancerCare Manitoba, Winnipeg, Manitoba; and BC Cancer Agency, Vancouver, British Columbia, Canada

Abstract

Purpose

Intravenous (IV) compounding safety has garnered recent attention as a result of high-profile incidents, awareness efforts from the safety community, and increasingly stringent practice standards. New research with more-sensitive error detection techniques continues to reinforce that error rates with manual IV compounding are unacceptably high. In 2014, our team published an observational study that described three types of previously unrecognized and potentially catastrophic latent chemotherapy preparation errors in Canadian oncology pharmacies that would otherwise be undetectable. We expand on this research and explore whether additional potential human failures are yet to be addressed by practice standards.

Methods

Field observations were conducted in four cancer center pharmacies in four Canadian provinces from January 2013 to February 2015. Human factors specialists observed and interviewed pharmacy managers, oncology pharmacists, pharmacy technicians, and pharmacy assistants as they carried out their work. Emphasis was on latent errors (potential human failures) that could lead to outcomes such as wrong drug, dose, or diluent.

Results

Given the relatively short observational period, no active failures or actual errors were observed. However, 11 latent errors in chemotherapy compounding were identified. In terms of severity, all 11 errors create the potential for a patient to receive the wrong drug or dose, which in the context of cancer care, could lead to death or permanent loss of function. Three of the 11 practices were observed in our previous study, but eight were new. Applicable Canadian and international standards and guidelines do not explicitly address many of the potentially error-prone practices observed.


Conclusion

We observed a significant degree of risk for error in manual mixing practice. These latent errors may exist in other regions where manual compounding of IV chemotherapy takes place. Continued efforts to advance standards, guidelines, technological innovation, and chemical quality testing are needed.

INTRODUCTION

The past few decades have brought a growing awareness of the effect of human error on health care, including in oncology

practice. Although several studies have established rates of error, or active failures, with chemotherapy,¹⁻⁴ theorists such as Reason⁵ have highlighted the importance

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of studying working conditions so that the underlying potential human failures, or latent errors, can be remedied. For example, whereas an active failure would be the selection and use of the wrong drug during chemotherapy mixing, a latent error would be the storage of look-alike drugs beside each other.

In 2014, members of our team published an observational study that described three types of previously unrecognized latent chemotherapy preparation errors in Canadian oncology pharmacies.⁶ The following potentially catastrophic compounding errors would not have been detectable if they occurred:

1. For drugs that require reconstitution, the incorrect volume or type of diluent could be injected into a chemotherapy vial because quality checks of reconstitution were not in routine use and may not always be effective when they are used.
2. The incorrect medication could be selected and drawn into a syringe but the correct vial shown to the pharmacist during their check because multiple drugs often were stored in proximity in the biologic safety cabinet (BSC).
3. The wrong patient-specific drug label could be applied to a correctly mixed bag because labels often were not physically affixed to the bag in which the drugs were to be injected until after mixing was complete.

Since, intravenous (IV) compounding safety has garnered increased attention as a result of some high-profile incidents,^{7,8} awareness efforts from the safety community,⁹⁻¹¹ and increasingly stringent practice standards.¹²⁻¹⁶ Meanwhile, new research with more-sensitive error detection techniques than in past studies has continued to reinforce that error rates with manual IV compounding are unacceptably high.¹⁷⁻¹⁹

As did our original work, this study used human factors-informed observation and analysis to identify and describe latent errors. Whereas our previous study explored latent errors across the entire chemotherapy delivery pathway from ordering to administration, the goal of this study was to gain a deeper understanding of latent errors specific to manual chemotherapy compounding practices.

METHODS

Field observations were conducted in four cancer center pharmacies in four Canadian provinces from January 2013 to February 2015. Sites were chosen from among the organizations that had provided support for the study. Production ranged from 15 to 300 chemotherapy mixes per day.

At each site for approximately 12 hours over a period of 2 to 3 days, human factors specialists observed and interviewed pharmacy managers, oncology pharmacists, pharmacy technicians, and pharmacy assistants as they carried out their work. The scope of observation was from the point the pharmacy received a chemotherapy order to when a completed product was ready to be sent for administration. Emphasis was on potential errors that could lead to outcomes of wrong drug, wrong dose, or wrong diluent. Sterility of the product and safe handling of hazardous drugs, although important, were not the focus.

By using the method of contextual inquiry²⁰ observers asked questions; took detailed notes; collected artifacts (eg, policies, worksheets, de-identified labels); and captured photographs of equipment, materials, and the environment. A spreadsheet was used to document each site's production practices consistently and followed the format of a task analysis.²¹ In other words, generalized steps and substeps in chemotherapy production were listed in rows, and practice details for each site were listed in columns. Latent errors were identified by reviewing each practice and asking, "Given human limitations such as memory, attention, and cognitive biases, is an error possible?"

RESULTS

Various approaches to six preparation-related steps were observed among the four sites (Table 1).

Latent Errors

As expected given the relatively short observational period, no active failures or actual errors were observed. However, 11 latent errors were identified and are grouped herein by process category. All three of the latent errors described in our first study⁶ were observed again (identified with an asterisk), and eight new latent errors were identified. In terms of severity, all 11 latent errors created the potential for a patient to receive the wrong drug or dose, which in the context of cancer care, could lead to death or permanent loss of function. In risk management frameworks, such as Healthcare Failure Mode and Effect Analysis,²³ this level of severity would be classified as catastrophic.

Transcription

Transcription comprises the entering of details from the physician's order into the pharmacy computer system. Pharmacy systems are used downstream from the ordering process, including for the critical step of generating labels, which often act as compounding instructions.

Table 1. Approaches to Compounding Intravenous Chemotherapy in Four Canadian Oncology Pharmacies

Step	Site A	Site B	Site C	Site D
Transcription	Technician manually transcribes prescription from CPOE system to pharmacy system	Technician manually transcribes prescription from preprinted order to pharmacy system	No transcription required: same system used for CPOE and pharmacy	Technician manually transcribes prescription from CPOE system to pharmacy system
Staging	One mix per bin	All patient's mixes in one bin	All patient's mixes in one bin (bin shortage)	One mix per bin
	Staging done in batches, one patient at a time	Staging done in batches, one patient at a time	Staging done in batches, one patient at a time	Staging done in batches, up to 10 mixes at a time
	Systematic and consistent check of staging done by stager and then mixer against a worksheet	No systematic or consistent check of staging	No systematic or consistent check of staging	Stager weighs diluent bag as precheck Consistent informal check of staging
Reconstitution	Drug-specific reconstitution worksheet is staged into bin	General reconstitution reference for all drugs to the right of the BSC	Reconstitution information included on mixing label	Drug-specific reconstitution worksheet staged into bin with mix
	Systematic and consistent check of reconstitution done by pharmacist by using worksheet	Technician or pharmacist usually confirms contents of syringes before injection into vial	Pharmacist visually verifies correct diluent, volume, and vial of powder	No extra checks done in clean room Pharmacist looks at empty diluent bag as part of final verification outside clean room
Mixing	Only one mix at a time in BSC	Usually one mix at a time in BSC, but if STAT order comes through, it goes in BSC with current mix	One patient's mixes at a time in BSC	Only one mix at a time in BSC
	Partially used vials stored to the left of mixing mat	Partially used vials stored inconsistently within BSC	Partially used vials stored inconsistently within the BSC	Partially used vials removed after every mix
	As many syringes as needed used to create total volume	As many syringes as needed used to create total volume	As many syringes as needed used to create total volume	One syringe reused as many times as necessary to create total volume
Verification	Pharmacist visually inspects full syringes before drug injected into container	Mixer inspects own syringes	Pharmacist visually inspects full syringes before drug injected into container	Mixer inspects own syringes
	Pharmacist verbally states drug information while mixer remains silent	Syringe pullback variant ²²	Mixer states name and volume of drug while pharmacist confirms	Syringe pullback variant: used vial(s) and syringe inspected by pharmacist outside clean room; weight of mixed bag compared with premixed weight
Label application	Mixing and administration labels put into mix-specific bin	Mixing and administration labels placed in bin with all patient's mixes	Mixing and administration labels into mix-specific bin Mixing label in plastic bag taped to final container	Mixing and administration labels put into mix-specific bin
	Administration label is affixed after mix wiped and removed from BSC and before final pharmacist verification	Administration label affixed after mix wiped and removed from BSC and before final pharmacist verification	Administration label affixed after mix wiped and removed from BSC and before final pharmacist verification	Administration label affixed after mix has left clean room and pharmacist has done final verification

Abbreviations: BSC, biologic safety cabinet; CPOE, computerized prescriber order entry; STAT, without delay.

1. Manual transcription of prescription into pharmacy system: In three of the four sites, someone (usually a technician) manually transcribed the chemotherapy prescription details into the pharmacy system, even when the systems were both electronic (two of four sites) because these systems did not interface with each other. Compared with electronic transcription, human transcription is error prone.²⁴ If an error in transcription were to occur, it has the potential to propagate downstream through the system, meaning that a patient could receive a mix that contains any type of error, including wrong drug or wrong dose. Although these sites had transcription checks in place, human error-checking processes are not fail-safe^{25,26} and were labor intensive.

Staging

Staging encompasses the selection and grouping of materials for compounding before their entry into the BSC. All sites used bins/baskets for staging. During staging, the wrong materials could be chosen or grouped, which can introduce new errors, such as wrong drug, wrong diluent, or wrong dose (eg, if wrong-sized syringes are chosen, the mixer may misinterpret the mixing volume).

2. More than one mix staged in each bin. Two of the sites staged materials for one patient in a single bin, which often meant multiple mixes in one bin. Staging more than one mix per bin creates the potential for the wrong drugs, syringes, final containers, mixing instructions, and/or labels to be loaded into the BSC, which would lead to mixing errors.⁶
3. No systematic check of staging. Two of the sites did not consistently use systematic staging double-checks. A third site used checks, but they were not systematic. Although double-checks are not fail-safe, they can reduce the potential for error, especially when done independently and with well-designed supportive tools, such as a checklist.^{25,26} Without an effective staging check, a staging error will likely propagate downstream into mixing and beyond.

Reconstitution

Some chemotherapy drugs must be reconstituted with a precise type and quantity of diluent before being used for compounding. Some manufacturers package the drug with the exact diluent to be added, whereas others require the manual

selection and measurement of diluent from the pharmacy's stock. Each pharmacy had both types of drugs for reconstitution.

If an error in reconstitution occurs, no way of detecting it downstream may exist and could result in a significant dose error. Drug-specific reconstitution protocols and independent reconstitution checks, therefore, are critical.

4. No drug-specific reconstitution instructions staged with mix. One site had a single document outside and to the right of the BSC that listed all the drugs' reconstitution instructions. Therefore, a technician would need to lean outward and scan the whole document to find a specific drug's instructions and then interpret them correctly. However, the document was not always referenced, and even when it was, the visual scanning process meant that it would be easy to read the wrong instructions, which would lead to a reconstitution error.
5. No live verification of reconstitution.* Another site had no live inspection of reconstitution: The pharmacist verified reconstitution only after the completed admixture had left the clean room and used proxy methods, such as examination of the diluent bag to estimate correctness (see Verification). Proxy methods of verification could fail, which would lead to a reconstitution error.

Mixing

Mixing entails the combination of precise volumes of drug(s) and a base solution into a final container, such as a diluent bag, bottle, or syringe. Having more than one mix in the BSC at once could result in errors: The technician could withdraw from the incorrect vial of chemotherapy drug but show the correct vial during verification (or have the check fail), and labels could be misapplied.

6. More than one mix at a time in BSC.* The two sites that staged patients' mixes in the same bin also sometimes had one or more mixes in the BSC at once (Fig 1). A mix-up of drug, dose, and/or label, therefore, was possible.

One of the challenges with mixing is the management of partially used vials of chemotherapy drugs throughout the day. Two options exist: Keep the vials in the BSC until they are empty or remove partially used vials as soon as the mix is complete then return them to the BSC the next time they are needed. Keeping vials in the BSC means that they have less exposure to environmental contaminants and less chance of a spill; however, a resulting risk of error exists.



Fig 1. Several mixes are in the biologic safety cabinet. Labels are paired with associated final containers by using tape and zip-top bags.

7. Accumulation of partially used vials in BSC. Three of the four sites chose to avoid removing partially used vials of chemotherapy drugs from the BSC until the end of the day. If there was a partially used vial of the target drug available in the BSC, it would be used first, followed by a new vial. Of these three sites, two had inconsistent approaches to storage of the vials within the BSC, which makes mix-ups more likely. The risk of having additional high-risk vials in the BSC along with the target vials is the same as having more than one mix at a time: The mixer could mistakenly choose one of these vials instead of the target vial for the mix but still show the correct vial during the check (and/or have the check fail).

Another challenge with mixing is the management of syringes.

8. Reuse of same syringe to create total dose. To reduce environmental waste, one site reused a syringe as many times as necessary to achieve a target volume. Thus, for example, to achieve a total volume of 24 mL, it might use a 10-mL syringe to withdraw 8 mL, inject it into the bag, and repeat twice more. The risk with this approach is the possibility of losing track and injecting too little or too much drug into the final container. The person who checks the mix also could lose track or make a mistake

in mental math. Without being able to see all the syringes at once, reliable confirmation of the total volume is difficult.

Verification

Verification of the mixing steps is a widely required and performed practice, but the way in which a verification is performed is critical to safety. Small differences in practice can have a large effect on error detection.

9. Proxy methods of mixing verification. Two of the four sites used a variant of the denounced syringe pullback method.²² At both sites, the mixer would withdraw the drug into the syringe and inject it into the final container without direct observation by a second individual. With the drug still in the syringe, the technician would write the short form of the drug name and mark the line of the drug volume on the barrel of the syringe. The syringes and empty vials would be inspected later. At one site, a mixing assistant would check empty syringes and vials before the mix left the clean room, and at another site, a pharmacist would check empty syringes and vials outside the clean room as part of the final verification. This same site also used a weight-based check where the premixing weight of the bags was documented during staging and the post-mixing weight checked against an estimated target weight during the final verification. Although this weight-based check could catch potential mixing errors, some errors could easily be missed. For example, an error in reconstitution could be made but the correct volume of drug withdrawn, or two errors could cancel each other out to create the correct weight.
10. Verification biased by drug and dose being spoken aloud. At two sites, the mixer spoke aloud the name and volume of drug just withdrawn, for example, “five of cyclophosphamide.” Telling the checker what to expect can create confirmation bias: The checker may accept what has been stated aloud rather than see what is being shown. For example, if the mixer believed that he or she had withdrawn (and, therefore, spoke aloud) cyclophosphamide but had withdrawn cyclosporine, the checker might not notice the error. All downstream visual checks would subsequently fail because the final container and the label would be correct.

Labeling

Application of the final label is a critical activity to preventing errors. If a mix has been prepared according to instructions

but the wrong label applied, a patient could get the entirely wrong mix and receive his or her own drug out of sequence and at the wrong rate.

11. Label applied after mix has left BSC.* At two of the four sites, administration labels were affixed after the mix had left the BSC, which created the potential for the labels to become lost and/or mixed up and, ultimately, applied to the wrong final container.

DISCUSSION

In this study, 11 latent errors in chemotherapy compounding that could have catastrophic consequences to patients were observed. Three of the 11 problematic compounding practices had been observed in our previous study (indicated with an asterisk), but eight were new:

1. Manual transcription of prescription into pharmacy system
2. More than one mix staged in each bin
3. No systematic check of staging
4. No drug-specific reconstitution instructions staged with mix
5. No live verification of reconstitution*
6. More than one mix at a time in BSC*
7. Accumulation of partially used vials in BSC
8. Reuse of same syringe to create total dose
9. Proxy methods of mixing verification
10. Verification biased by drug and dose being spoken aloud
11. Label applied after mix has left BSC*

Relevant regulatory standards do not address these issues. Canadian standards published by Accreditation Canada and the National Association of Pharmacy Regulatory Authorities make no reference to the avoidance of these practices.^{15,27,28} The equivalent American standards of USP797¹² and USP800²⁹ are similar in this respect. Although intended to address safety, most of the content is heavily focused on protecting the final sterile product from contamination and/or on protecting the environment and staff from hazardous exposure.

Other practice guidance documents cover a few of the observed latent errors, although most medication error prevention statements are too high level to address the specific issues that we observed. Safety standards from ASCO,¹⁴ error prevention guidelines from the American Society of Hospital Pharmacists,³⁰ and standards of practice from the Canadian Association of Pharmacy in Oncology³¹ do not have statements that directly address the issues. The Canadian Society

for Hospital Pharmacists compounding guidelines³² address issues 3, 6, and 11. The issue of storage of partiality used vials (7) also is addressed somewhat in these guidelines with the statement “used syringes, bottles, vials, and other supplies shall be removed from the critical area in the primary clean air device.” The International Society for Oncology Pharmacy Practice standards of practice³³ refers to issue 3 (checking staged materials before they enter the BSC). Its safe compounding guidelines¹³ exclusively focus on error prevention in compounding and directly address four of the 11 the latent errors, specifically 2, 6, 9, and 11. Thus, no one guideline addresses all issues, a combination of guidelines address some of the issues, and nothing specifically addresses the issues of manual transcription of prescription to pharmacy system, no drug-specific reconstitution instructions with mix, no live verification of reconstitution, reuse of same syringe to create total dose, and verification biased by drug and dose being spoken aloud.

Practice standards must be updated to include statements that address the specific mechanisms of latent error observed in the current study. Although the balancing of requirements for sterility and hazardous protection with those of error prevention may be challenging, the former issues are being given a disproportionate amount of attention in these documents.

Although standards and guidelines are critical elements of a safe system, they are not sufficient. Automated compounding processes from robotics to bar coding and gravimetric weighing, with built-in error prevention functions, have shown promise in error reduction^{18,19,34-36} and may address or eliminate many of the latent errors observed in the current study. Meanwhile, unlike other industries with high-risk production processes, chemotherapy compounding has not adopted live quality control mechanisms that confirm the actual contents of the prepared compounds (with the exception of a few French sites).^{37,38} Use of techniques such as spectrometry, high-performance liquid chromatography, and sensors should be implemented to catch errors that do slip through.

In addition, it is technologically feasible for all order-based information technology systems, such as computerized prescriber order entry, and pharmacies to interface, yet often they do not, which can lead to transcription errors. This is unacceptable.

Although these changes are essential, they take time and significant resource investments. Therefore, ongoing observational research and local quality improvement initiatives that identify and address additional latent errors are critical

to the overall reduction of preventable errors with chemotherapy. In addition, interim low-technology strategies, such as drug-specific compounding worksheets,³⁹ should be considered.

This observational study included a small number of sites in only four Canadian provinces. As a result, the opportunity to observe many other latent errors likely was missed. However, in this small sample, light has been shed on practice issues that are not addressed by most current safety mechanisms. Another limitation is that no actual errors were observed, which means that it was not possible to know how likely they are to occur. However, for such high-risk activity as chemotherapy compounding, the anticipation and addressing of issues before they result in patient harm are essential.

In conclusion, in this observational, human factors–based study of four Canadian oncology pharmacies, a significant degree of risk for serious error in manual mixing practice was observed. That these latent errors exist in other regions where manual compounding of IV chemotherapy takes place is reasonable to assume. Much room for improvement in IV compounding exists. Continued efforts to advance standards, guidelines, technological innovation, and chemical quality testing are needed. **JOP**

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Authors' Disclosures of Potential Conflicts of Interest

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Author Contributions

Conception and design: Rachel E. Gilbert, Melissa C. Kozak, Roxanne B. Dobish, Vishal Kukreti, Anthony C. Easty, Patricia L. Trbovich

Administrative support: Rachel E. Gilbert, Heather A. Logan

Provision of study materials or patients: Roxanne B. Dobish, Vishal Kukreti, Venetia C. Bourrier, Paul M. Koke

Collection and assembly of data: Rachel E. Gilbert, Melissa C. Kozak, Roxanne B. Dobish, Venetia C. Bourrier, Paul M. Koke

Data analysis and interpretation: Rachel E. Gilbert, Melissa C. Kozak, Roxanne B. Dobish, Paul M. Koke, Vishal Kukreti, Heather A. Logan, Anthony C. Easty, Patricia L. Trbovich

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Corresponding author: Rachel E. Gilbert, MA; e-mail: rachel@rachelgilbert.ca.

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Vishal Kukreti

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