RESEARCH BRIEF

Acquisition and Retention of Sterile Compounding Accuracy Skills

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Objective. To determine the accuracy of dose of pharmacy students' parenteral sterile preparation skills and to measure pharmacy students' skill retention 1.5 years later.

Methods. An exercise was designed to assess each student's accuracy in compounding a sterile preparation with the correct potency during a second and then third year course.

Results. Initially, the mean (standard deviation) of 141 students' compounded preparation dose was not significantly different than the desired dose. Additionally, 91.5% of products were within 10% of the desired dose. In the follow-up activity the next academic year, the mean dose was not significantly different than the original compounded dose. Similarly 92.9% were within 10% of the desired dose.

Conclusion. Students' overall accuracy of sterile compounding was good initially and well-retained more than a year later, with more than 90% of students being within 10% of the desired dose in both courses.

Keywords: sterile compounding, compounding accuracy, student retention

INTRODUCTION

The safe and accurate preparation of parenteral products is central to the responsibilities of pharmacists and pharmacy technicians. Based on multiple recent reports of fatal and non-fatal compounding errors,¹ it is imperative that pharmacists can safely and accurately prepare both sterile and non-sterile products. Safe sterile product preparation includes the ability to prepare and dispense products of correct ingredient identity, purity, strength and sterility.^{2,3} While resources are available to guide practitioners in the correct compounding of sterile preparations,¹⁻⁴ pharmacy schools also play a role in educating pharmacy students on the baseline competencies related to sterile product preparation. A 2007 report documented the amount and content of sterile product education which is provided in schools and colleges of pharmacy across the United States.⁴ This is an important expectation of the Accreditation Council for Pharmacy Education (ACPE), specifically articulated in Appendix 1 of the 2016 revision of the ACPE Standards.⁵

A 2010 survey evaluating the compounding curriculum within pharmacy schools in the US identified the need for increased quantitative analysis of student

compounded preparations within the compounding curriculum.⁶ The survey indicated that in a pharmacy school compounding course, the evaluation of compounded formulations was mainly by direct observation (33.5%) or qualitative assessment (13.8%), while only 8% utilized a quantitative assessment.

Previously published reports describe the quantitative analysis of pharmacy students' non-sterile compounded formulations including solutions, capsules, suppositories, effervescent powders, tablet triturates, pluronic lecithin organogels (PLO gels), and medicated sticks.⁷⁻¹⁴

While study design and results varied, many demonstrated that students were unable to consistently compound non-sterile products within an acceptable 10% error range as identified by the United States Pharmacopeia (USP) chapter 795 standards.^{15,26} These results are consistent with both the 2001 and 2006 Federal Drug Administration (FDA) surveys of non-sterile products from pharmacies across the US.^{16,17} In the 2001 survey, 29 samples were evaluated for concentration testing with nine (31%) failing to meet a compounding standard within 10% of the label claim; the 2006 survey analyzed 36 samples, with 12 (33%) falling outside the 10% acceptable window. Another study quantitatively analyzed a small number of oral preparations compounded by pharmacy students in two consecutive years and demonstrated that 13% (4 out of 32) and 26% (6 out of 23) of the

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compounded sterile preparations had an accuracy error greater than or equal to 11% from the targeted concentration.¹⁸

Flynn and colleagues assessed the error rates in compounded sterile products at five hospitals across the US.¹⁹ A product was deemed to have been prepared in error if it met any of the following criteria: use of an unauthorized drug, wrong dose, wrong base solution content or volume, omission of a component, wrong form of delivery, incorrect reconstitution procedure, or wrong preparation technique. Quantitative assessments of the products were not performed. A mean error rate of 9% was identified, with the authors judging two out of every 100 errors to be potentially clinically important. Microbial contamination rates of student-prepared sterile preparations have also been reported. Isanhart and colleagues²⁰ analyzed low and medium risk level media fill tests prepared by 84 P2 students. Near the end of a 16-week one-credit parenteral laboratory course, all students were able to prepare six compounded sterile products in a syringe without microbial contamination. Two 2005 studies compared contamination error rates of pharmacists and technicians while compounding sterile products. Trissel and colleagues found that pharmacists' compounding resulted in a slightly lower contamination rate (4.4%) than that of technicians (6.2%).²¹ Thomas and colleagues did not identify a statistically significant difference in microbial contamination rates in a cleanroom versus one not meeting USP chapter 797 requirements, but did identify a statistically significant reduction in microbial contamination of products prepared by pharmacists as opposed to technicians, concluding that aseptic technique of the compounder is more important than the environment.²²

An American Association of Colleges of Pharmacy (AACP) Compounding Task Force assessed the compounding education provided by AACP member institutions in a 2010 survey, and made recommendations based on survey results.⁶ The task force recommended that compounding education should be included in the pharmacy education curriculum, with a strong indication of the need for one semester of compounding education in each of the first two academic years. Current placement of sterile product compounding education in the pharmacy school curriculum has not been documented. Previous studies have concluded that multiple testing of a skill both enhances learning and improves long-term retention.^{23,24} Didactic instruction to students complemented with frequent skill assessment may play a role in skill retention, increasing accuracy of product preparation and ultimately, improved patient therapy.

Eley and Bernie assessed P2 students' ability to compound capsules 12 months after completing a compounding course.²⁵ The authors estimated that students achieving

a score of 80% or better on the activity would indicate that skill competence had been maintained. However, only 17% of students were able to meet this benchmark. The authors concluded that pharmacy students' level of competency and retention of knowledge with respect to compounding capsules was not adequately retained after a 12-month period.

Faculty at Concordia University Wisconsin School of Pharmacy assessed P2 and P3 students' acquisition and retention of sterile product preparation skills through the use of quantitative analysis. The primary objective of this project was to determine the accuracy of students' parenteral product preparation skills as measured by the potency of their products. The secondary objective was to measure the students' retention of their acquired skills later in the curriculum.

METHODS

The Phar 426 (Advanced Pharmaceutical Preparation) course provides students with the skills and knowledge required for safe and accurate sterile compounding. This required course is offered during the fall semester of the P2 year. Each class consists of approximately 90 students. The course includes an hour-long weekly classroom-based learning session and a one and a half hour long weekly laboratory-based learning session. Initially, the students were taught the content of USP Chapter 797 and the fundamentals of aseptic technique. The students received four weeks of hands-on aseptic technique practice before their aseptic technique was evaluated utilizing an aseptic technique rubric. The aseptic technique rubric was provided to the students at the beginning of the semester with the expectation that they will be graded with it. This rubric was adapted from a previously published aseptic technique rubric with mild or moderate wording changes.²⁷

The laboratory activities were completed in a training room designed to serve as a simulated compounding environment. The room consists of six laminar airflow workbenches and two compounding aseptic isolators. Only 14 students had adequate space to compound, which represents the maximum number of students allowed to compound at any given time.

Given the objectives of this project, a laboratory exercise was designed to quantitatively assess each student's accuracy in compounding a sterile preparation. The exercise required a pharmacy student to withdraw 2 mL of ondansetron injection USP (concentration of 2 mg/mL; total ondansetron dose of 4 mg) using a 3 mL syringe from a 20 mL multi-dose vial and injecting the dose into a 50 mL 0.9% sodium chloride injection USP IV bag. Although other activities in this course require

students to calculate doses, the specific objectives of this activity were only to accurately and aseptically compound this preparation. All calculations and standard operating procedures were provided to the students. The students were aware that their aseptic technique was being observed. However, they were not aware that their product would be subsequently analyzed for accuracy of the compounded ondansetron dose.

Additionally, an assessment of skill retention of accurate compounding of a sterile preparation was done with these students three semesters later in the two credit Phar 572 (Applied Patient Care) required course. This course is offered to P3 students in the spring semester and includes a 110-minute laboratory component weekly and several 50-minute lecture sessions over the course of the semester. It is a patient-centered course that uses simulated patient scenarios and case studies to build students' foundational skills in drug information retrieval, patient interviewing, patient education, care plan development and delivery, and critical thinking in the context of pharmacy's multiple disciplines. Cases are designed so that students integrate the knowledge learned in other concurrent courses as well as that from previous semesters of the curriculum. One of the integration activities occurs during week three's laboratory session in which students are asked to compound the same ondansetron product they prepared one and a half years earlier during the Phar 426 course. The premise for this exercise was for students to complete a self-assessment of the aseptic techniques used in their compounded preparations. They also were not aware that their preparations would be subsequently analyzed for accuracy of compounding the ondansetron sterile preparation.

Before the required ondansetron sterile compounding in Phar 572, students were instructed to review a video on proper aseptic technique, complete any needed calculations and develop a compounding procedure in preparation of the actual in-laboratory sterile compounding activity. During the laboratory session, students had 30 minutes to prepare the sterile product, review their video of their aseptic technique and complete a self-assessment on their compounding. Students were assessed solely on the completion of compounding a sterile preparation and completion of a self-assessment of their aseptic technique.

To quantitatively assess the students' products in both Phar 426 and Phar 572 courses, a rapid ultraviolet (UV) analytical method was developed using a UV spectrophotometer with a sipper attachment and quartz flow cell to measure the concentration of ondansetron in 0.9% sodium chloride IV bags prepared by the pharmacy students. Calibration standards required for the analysis of student products were made by diluting different volumes

(from 0.5 to 3.0 ml) of Ondansetron Injection, USP with 0.9% Sodium Chloride Injection, USP in 50 ml volumetric flasks. The calibration standards gave reliable linear calibration curves with R-squared coefficients (R^2) ranging from 0.99 to 1.00. Based on the students' measured ondansetron concentrations and the actual IV bag volumes, the dose of delivered ondansetron was calculated.²⁸ The assays were completed by a faculty member (PZ) with help from upper-level P3 and P4 students assisting in an on-campus laboratory.

The primary outcome of this project was to quantitatively analyze the ondansetron dose of the pharmacy students' compounded preparations made during their P2 year in the Phar 426 course and again during their P3 year in the Phar 572 course. The doses were calculated from the measured ondansetron concentrations and IV bag volumes utilizing the developed UV standard curves. The statistical comparison of students' average compounded doses relative to the expected 4 mg ondansetron dose was evaluated with a student's *t*-test.

The secondary objective of this project was to measure students' skill retention by analyzing the proportion of students making products within $\pm 5\%$ (expected margin of the assay) and $\pm 10\%$ (expected acceptable margin in most practice settings) of the intended 4 mg dose. The secondary outcome comparing the mean doses in Phar 426 versus Phar 572 was analyzed with a student's *t*-test. The secondary outcome comparing the proportion of products within 5% and 10% between Phar 426 and Phar 572 was analyzed using the Chi-Square Test. The project has been determined to be exempt by Concordia University Wisconsin's Institutional Review Board.

RESULTS

Over the course of the 2012-2013 and 2013-2014 academic years, a total of 141 P2 students compounded ondansetron 4 mg sterile preparations in the Phar 426 laboratory using a 3 mL syringe for their ondansetron dose accuracy and transfer from the ondansetron vial to a 0.9% sodium chloride IV bag. Over the course of the 2013-2014 and 2014-2015 academic years, a total of 154 P3 students in the Phar 572 lab compounded the same ondansetron 4 mg sterile preparation prepared one and a half years earlier in Phar 426 lab.

For the 141 sterile preparations compounded in the Phar 426 lab, the mean (SD) ondansetron dose compounded by the students was 4.03 (0.45) mg. This was not significantly different than the 4 mg dose desired for this product ($p = .50$). The number of students who were within 10% of the desired 4 mg dose was 129 (91.5%) and the number within 5% of the desired dose was 113 (80.1%). The minimum and maximum erroneous doses in

the compounded preparations were 3.33 mg and 7.18 mg, respectively.

For the 154 sterile preparations compounded in the Phar 572 lab, the mean ondansetron dose compounded by the students was 3.96 (0.51) mg. This was not significantly different than the 4 mg dose desired for this product ($p=.36$). The number of students who were within 10% of the desired 4 mg dose was 143 (92.9%). The number of students who were within 5% of the desired 4 mg dose was 123 (79.9%). The minimum and maximum erroneous doses in the compounded preparations were no drug present and 5.01 mg, respectively. There was no statistically significant difference between the accuracy data between the Phar 426 course and the Phar 572 course. Table 1 summarizes the secondary outcomes data regarding sterile compounding accuracy skill retention from the Phar 426 P2 course to the Phar 572 P3 course.

DISCUSSION

To our knowledge, this was the first study to examine the accuracy of students' parenteral compounding skills by measuring the dose of their compounded sterile preparations, their retention of their acquired skills later in the curriculum and the comparison between a cohort's skill acquisition and retention. Overall, the study demonstrated students were able to compound a sterile preparation accurately with their initial course instruction and retain those accuracy skills later in the curriculum, with no difference in the overall accuracy between the two courses. Once students acquire the experience of syringe and dose preparation accuracy, the study suggests the knowledge and skill will continue past the initial learning period. There are a few limitations regarding this study and its direct application to practice and pharmacy school curriculums. Since all the preparations were compounded in a classroom setting, the students knew that none of the preparations would actually be administered to a patient. Thus, students may have been less accurate in their compounding due to the knowledge that inaccuracy would not lead to clinical patient harm. Additionally, the students were never previously told that their compounded preparations would be analyzed for accuracy in potency nor

was this an assessment they would suspect. Although compounding errors like air bubbles would be noted visually by an instructor, subtle difference in volume withdrawal from vials or ampules would not likely be caught without a quantitative assessment. Lastly, the exercises were not timed. Students did not have the typical compounding time constraints observed during the compounding of preparations in a typical pharmacy practice environment which should allow students more time to be more focused on accuracy and good aseptic technique.

Another consideration for implementation of a quantitative aseptic product accuracy assessment into sterile compounding training would be the resource implications. While the material cost of the preparations and assays was very low, the time required to develop the assay standard curve and running the individual samples could be significant, particularly if this was repeated multiple times throughout the curriculum. The material cost for each student's preparation included the cost of an intravenous diluent bag, the drug used in the assay and the consumable supplies, such as the syringes, needles, alcohol pads, to prepare the one compounded sterile preparation. The material cost for the assay development included the cost of four vials of the drug and six intravenous diluent bags. Once the calibration curve standard was developed, each student's preparation was analyzed in two to three minutes. Instrumentation cost was negligible as it was already available as a staple of research in pharmaceuticals.

However, the implementation of quantitative assessments in sterile compounding training may provide a valuable tool though limited data has been done on the baseline accuracy rates of sterile compounded dosage forms. USP has established that the acceptable range of most compounded preparations is typically $\pm 10\%$, or within the range of 90.0% to 110.0%.²⁶ Thus, for the Phar 426 and Phar 572 courses, 8.5% and 7.1%, respectively, of the students' sterile compounded preparations fell outside the USP's established acceptable range. Based on previous studies found regarding the quantitative accuracy of all compounded dosage forms,^{13,16-18} this study demonstrates higher accuracy rates regarding the compounding

Table 1. Accuracy of the Sterile Preparation Compounding in Phar 426 and Phar 572 Courses

	Phar 426 N=141 ^a	Phar 572 N=154 ^a	<i>p</i> value
Mean compounded dose (mg)	4.03	3.96	.26 ^b
Compounded preparations within 10% of 4 mg desired dose N (%)	129 (91.5)	143 (92.9)	.67 ^c
Compounded preparations within 5% of 4 mg desired dose N (%)	113 (80.1)	123 (79.9)	1.0 ^c

^a N=student's compounded preparations

^b student's *t*-test was used to determine significance

^c Chi-Square Test was used to determine significance

of the final concentration or dose in the preparation. However, based on a previous research regarding the observed compounding accuracy related only to sterile dosage forms, the accuracy of the students' compounded preparations was similar.¹⁹

There are various sources of error that may explain why some students made products significantly off from the intended dose of 4 milligrams of ondansetron, including even the potential failure to inject drug product into the secondary container as evidenced by one product reading with no active ingredient. However, it is beyond the scope of our study to identify a particular source of error. The more concerning piece would be if there was a systematic failure in either this activity or the ondansetron compounding recipe or equipment used. However, if a systematic error was involved, we would likely see this in the research data and nothing presents as such a problem. Acceptable accuracy in the compounded dose and skill retention was observed in our studies. Further studies need to be conducted to provide information regarding source of sterile compounding accuracy errors.

In both the Phar 426 and Phar 572 courses, the students' ondansetron compounding was recorded via video capture. This process was left the same in both courses to maintain a consistent and comparable environment for the students. In the Phar 426 course, the students ondansetron compounding was assessed for proper aseptic technique by instructor observation whereas in the Phar 572 course, the aseptic technique was not assessed by an instructor. While the video capture is accurate enough to observe gross manipulations and aids in the evaluation of aseptic technique including student challenges, it does not have high enough resolution to identify the volume inside a compounder's syringe. Future work with advanced imaging technology could aid in visualization of plunger location and air bubbles.

Due to the increased emphasis on sterile compounding training in practice and within schools of pharmacy, all schools of pharmacy should consider including quantitative sterile compounding accuracy checks as part of their curriculum for sterile compounding. While this assessment requires an expenditure of drug, supply and assessment cost, an evaluation of students' accuracy is essential when teaching and evaluating the precise art of sterile compounding. A curriculum could require successful quantitative assessments of students' compounded sterile preparations in order to pass the curriculum. However, if these assessments were completed multiple times throughout the teaching course, the requirement for unadulterated drug products and personnel assessment time would be a limitation to its incorporation into many school curriculums. If a school relied on

only one successful assessment for the student to pass the curriculum, the representation of a student's accuracy in sterile compounding could be skewed with just one worthy or substandard performance by that student. While this assessment provides another valuable tool in assessing student performance and skill in sterile compounding training, a thorough consideration of its role in each curriculum needs to be completed.

CONCLUSION

The average student's accuracy of ondansetron sterile compounded dose was found acceptable in both initial skill (Phar 426) and retained skill (Phar 572) since the accuracy errors of greater than 10% of the desired dose were consistent with other practice research studies and not significantly different between the courses. Limited data¹⁹ from hospital practice suggests this classroom error rate is similar to that seen in observed patient care settings which isn't surprising since many pharmacy students are also practicing sterile compounding in a paid work position or have the same level of training as pharmacy technicians in sterile compounding sites. Based on the previous literature and our observed study's error rates, all sterile compounding facilities, including pharmacy schools, should determine the accuracy error rate that is acceptable for their site, and ultimately, the patients who will receive those students' compounded sterile preparations in practice.

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