

# Accuracy in Prescriptions Compounded by Pharmacy Students

*Taking time to compound prescriptions accurately is worth the effort.*

## Abstract

Most compounded prescriptions are not analyzed to determine the accuracy of the employed instruments and procedures. The assumption is that the compounded prescription will be  $\pm 5\%$  the labeled claim. Two classes of School of Pharmacy students who received repeated instruction and supervision on proper compounding techniques and procedures were assessed to determine their accuracy of compounding a diphenhydramine hydrochloride prescription. After two attempts, only 62% to 68% of the students could compound the prescription within  $\pm 5\%$  the labeled claim; but 84% to 96% could attain an accuracy of  $\pm 10\%$ . The results suggest that an accuracy of  $\pm 10\%$  labeled claim is the least variation a pharmacist can expect when extemporaneously compounding prescriptions.

## Introduction

The extemporaneous compounding of pharmaceutical products requires that adequate care and time be taken to produce acceptable products. No shortcuts such as rounding off equivalents or approximating volumes by graduation marks on bottles, beakers, etc. should be taken in the compounding process. What are the consequences when these guidelines are not followed? That information is not readily available to the public, since few pharmacists or pharmacies analyze their compounded products before they are dispensed, or the analytical results are solely for inhouse quality assurance and not published.

One possible way of obtaining parallel information would be to study the compounding accuracy of pharmacy students. Although student compounders are less experienced than pharmacist compounders, students work in a controlled environment where they are repeatedly instructed and supervised on proper techniques and procedures that pharmacists tend to deemphasize in the "real world." Because of the constant supervision and attention to these details, student laboratory outcomes may be viewed as a possible representation of a number of pharmacist compounders.

Compounding has long been a part of the curriculum at the University of North Carolina School of Pharmacy. Over the last three years, compounding activities formally taught in a separate pharmaceuticals laboratory course have been incorporated into the pharmaceutical care skills laboratories, which have a primary focus of integrating elements of the core curriculum into a functional knowledge and skill base. The efforts of the School of Pharmacy are not in line with the majority of schools that have supplanted

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"wet labs" with clinical course work.<sup>1</sup> In fact, over the past two years, routine analysis of student products has been instituted in the course to provide feedback to the students, and to serve as an indicator of the need of remedial instruction. Typically, the concentration of the active ingredient in a compounded prescription is quantitated by high-pressure liquid chromatography (HPLC). A typical example of this effort has been published.<sup>2</sup> This analytical capability has also been used in some interesting legal cases involving compounding within the state of North Carolina,<sup>3,4</sup> which is of great interest and relevancy to the students.

This report summarizes two years' experience with a single student compounding exercise within the course sequence at the School of Pharmacy. The results show the product content variability when a number of students compound the same prescription and suggest a minimum variation pharmacists should expect. The report also shows the results that can be accomplished when adequate time and care are taken.

## Methods

The students' first exposure to compounding is a laboratory exercise in which they learn to use a prescription balance and then use the balance to compound the following prescription containing diphenhydramine hydrochloride:

Diphenhydramine hydrochloride	250 mg
Glycerin, USP	5 mL
Simple syrup, USP	30 mL
Vanillin solution 67 mg%	0.2 mL
Aqua Dist qs	100 mL

The exact procedure and instructions are available at [www.unc.edu/courses/phar0511/lab51/ex2/text.htm](http://www.unc.edu/courses/phar0511/lab51/ex2/text.htm).

The balance meets the requirements of the National Bureau of Standards Class III balance and is a Torbal torsion balance (either model DRX-2 or DRX-3) manufactured by Vertex Industries (Clifton, NJ). The students perform four basic tests<sup>5,6</sup> to learn how to correctly operate the balance, and to determine if the balance is operating within specifications. In the second part of the laboratory, the students compound the prescription using the balance to weigh diphenhydramine hydrochloride.

In the fall of 1996, the student products were analyzed both by ultraviolet (UV) spectrophotometry and HPLC. Samples were diluted 1:10 with water and read at 257 nm on a Genesys 5 UV/VIS spectrophotometer (Milton Roy Co., Rochester, NY). Initial UV scans had shown that alcoholic vanillin (0.5%) had absorbency maxima at 228 (0.874), 274 (0.494), and 306 (0.378). Simple syrup (5%) had absorbencies of 0.031 to 0.016 between 260 and 340 nm, and glycerin (10%) had an absorbency maximum at 276 (0.0636). It was anticipated that spectrophotometry absorbencies would

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**Table 1. Summary of Number of Students Who Compounded a Diphenhydramine Hydrochloride Prescription within 5% or 10% of the Labeled Claim.**

Year	First Attempt		Second Attempt	
	± 5%	± 10%	± 5%	± 10%
1996	29/102 (28%)	49/102 (48%)	63/102 (62%)	86/102 (84%)
1997	59/114 (52%)	88/114 (77%)	77/114 (68%)	110/114 (96%)

overestimate diphenhydramine concentrations. In an effort to offset that expectation, a blank of the vehicle (syrup, glycerin, vanillin) without diphenhydramine was used in the analysis.

The same samples were reanalyzed by HPLC using a published method.<sup>7</sup> Samples were read at 265 nm. Experiments showed that simple syrup, glycerin, and alcoholic vanillin in concentrations found

in the prescription did not produce interfering peaks. The mobile phase was modified slightly from the published method and was methanol (750 ml), tetrahydrofuran (50 ml), sodium dioctylsulphosuccinate (5.8 g), water (191 ml), and 85% phosphoric acid (1 ml). The mixture was then adjusted to pH 4.6 with ammonium hydroxide. Standard solutions of 0 to 5 mg/ml were prepared using diphenhydramine hydrochloride. All samples underwent a 1:10 dilution. Standard curves (Beer's Law plots) were constructed for each laboratory day from 0.0 to 0.5 mg/ml (which accounted for the 1:10 dilution of the original standards) with  $r^2$  values of > 0.991. The interday variation at 0.25 mg/ml (the target concentration) was 5.8% during the week the laboratory was operated.

## Results

For the 1996 fall semester class, a residual plot was made by taking the difference of the HPLC-determined and the spectrophotometry-determined diphenhydramine concentrations for each student's product. If the residual value was zero, then both methods resulted in the same concentration determination. The residual plot is shown in Fig. 1. All but two of the residual values were less than zero, meaning that almost all of the HPLC-determined concentrations were less than the spectrophotometry values. This was not an unexpected finding, as mentioned above. Thus, the HPLC results were used to determine the student performance.

In this class, 29 students (28%) had diphenhydramine hydrochloride concentrations that were  $\pm 5\%$  (2.5 mg/ml  $\pm$  0.125 mg/ml) of the labeled concentration (see Fig. 2). Forty-nine students (48%)

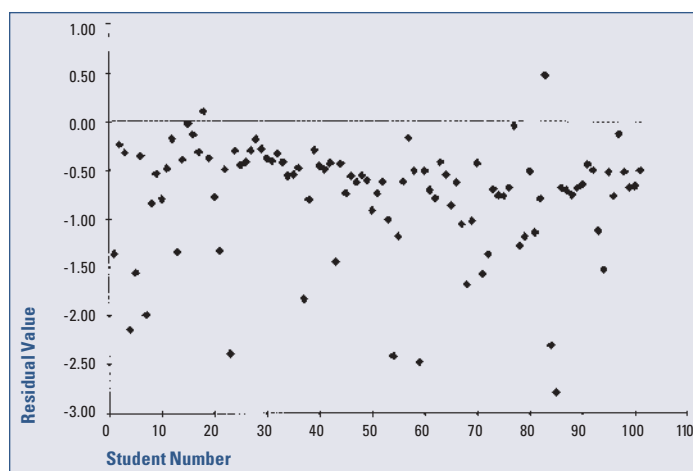


Fig. 1. Residual plot of difference between HPLC- and spectrophotometry-determined diphenhydramine hydrochloride concentrations for each student's product, 1996 fall semester.

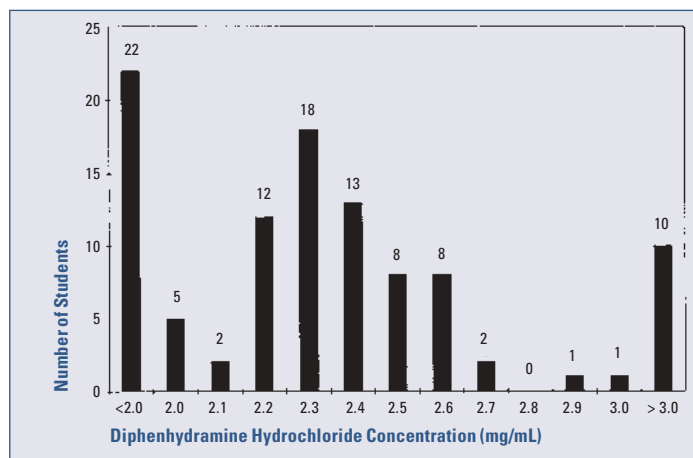


Fig. 2. Results of first attempt to compound a diphenhydramine hydrochloride prescription, 1996 fall semester.

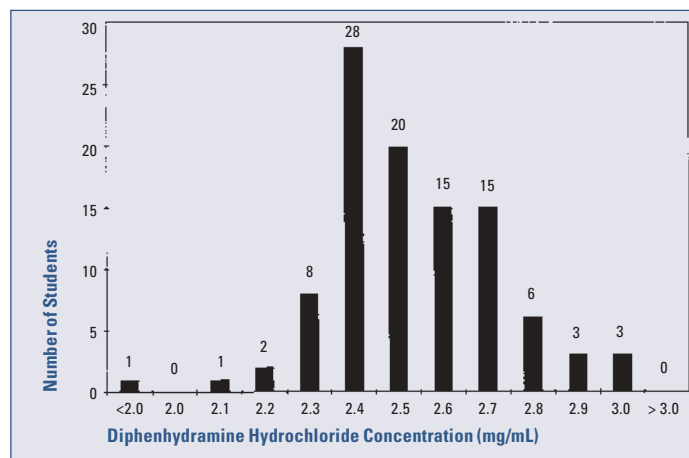


Fig. 3. Results of the remade products, 1996 fall semester.

had products that were  $\pm 10\%$  ( $2.5 \text{ mg/ml} \pm 0.25 \text{ mg/ml}$ ) of the desired concentration. Therefore, 53 of the 102 students (52%), over one half of the class, could not compound the prescription within the expected  $\pm 10\%$  of the labeled concentration. After these disappointing results were reviewed, it was decided that the entire class would remake the prescription the following week. The students were informed that their results were unacceptable, and that they were expected to take sufficient time and care to ensure that their remade products did not exceed the acceptable margin of error.

Following the make-up laboratory, the remade products were analyzed by the same HPLC method; the interday variation at  $0.25 \text{ mg/ml}$  was 2.8% during the "remake" week. Fig. 3 shows the results of the remade products and Table 1 summarizes the findings. Sixty-three students (62%) had concentrations that were  $\pm 5\%$  of the  $2.5\text{-mg/ml}$  value; 86 students had concentrations that were  $\pm 10\%$  of the value. Therefore, 84% of the students could compound the prescription with  $\pm 10\%$  accuracy.

For the 1997 fall semester class, the course requirement was made that students would come in on Friday afternoons to remake any prescriptions that were outside  $\pm 10\%$  the desired analyzed variable (e.g., drug concentration, pH, osmotic pressure, etc.). In this group of students, only 26 of the 114 students (23%) were outside the  $\pm 10\%$  range, meaning that 77% of the students could satisfactorily compound the diphenhydramine hydrochloride prescription on the first attempt (see Table 1 and Fig. 4). This strongly suggests that taking the time to compound is more important than level of experience with the prescription balance since both classes had the same degree of familiarization with the balance. Instead of having the entire class remake the prescription, only those outside the  $\pm 10\%$  range were required to repeat the exercise. Of those 26 students, 24 did complete the assignment; and all but two were within  $\pm 10\%$  (see Fig. 5).

## Discussion

The primary justification for the tremendous investment of time, manpower, and expense of analyzing all the student products was to instill in students the importance of adhering to tech-

niques to ensure product safety and accuracy. The first decision that had to be made was to define "acceptable" or "reasonable" student performance. Initial discussion centered on  $\pm 5\%$  of the labeled claim. Class III prescription balances have a sensitivity requirement of 6 mg, which gives a 5% error at 120 mg. Also, there is the often-mentioned  $\pm 5\%$  accuracy for compounded prescriptions, although the history of that "rule" is unknown. A review of *USPXXIII/NF18* monographs suggested that some monographs do not require  $\pm 5\%$  the labeled claim but accept wider ranges of 10% and 15%. Therefore, 10% variability was tentatively selected as being a sufficiently rigorous goal, but one that was attainable by the students. After 84% of the 1996 fall semester students compounded the diphenhydramine hydrochloride prescription within  $\pm 10\%$  on the second attempt, the 10% was adopted as the class expectation.

The evidence suggesting that taking time is more important than experience with the balance is seen with the first attempts of the two classes: 48% of the 1996 class, but 77% of the 1997 class, attained the  $\pm 10\%$  expectation. Yet both classes had the same familiarization with the balances; the only difference was that the 1997 class had the requirement that students would spend additional time in the laboratory if their products were unsatisfactory. Requiring additional time is a strong incentive to direct students to spend sufficient time and effort to correctly complete projects on the first attempt.

Returning to the original assumption, that student performance in a laboratory exercise could parallel the performance of a number of pharmacists compounding the same prescription in the "real world," then  $\pm 10\%$  the labeled claim would appear to be the expected variation. And, as further suggested in the introduction, there are little data available that would prove this assumption true or false. But one result is clear: taking the time to compound prescriptions accurately is worth the effort. The profession of pharmacy is involved in federal and state legislative struggles to preserve compounding as a non-Food and Drug Administration-regulated activity of pharmacists. As part of the individual pharmacist's contribution to that process, he or she should make every effort to com-

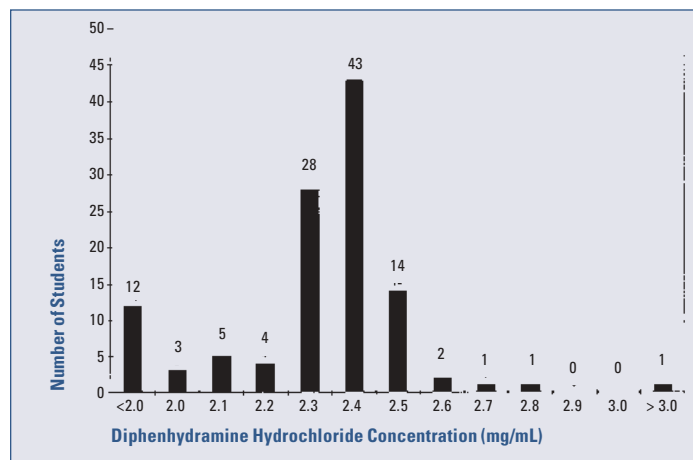


Fig. 4. Results of first attempt to compound a diphenhydramine hydrochloride prescription, 1997 fall semester.\*

\*Course requirement: makeup sessions for prescriptions outside  $\pm 10\%$  of desired analyzed variable.

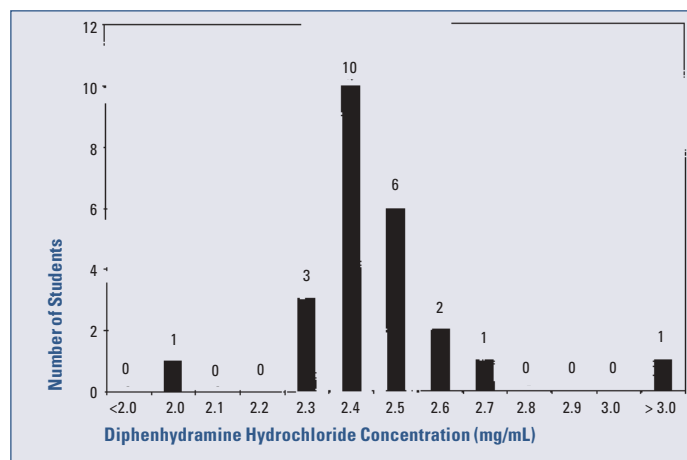


Fig. 5. Results of remade products, 1997 fall semester.

pound every prescription with the highest degree of accuracy possible. Taking the necessary time and care is the only way to achieve that goal.

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## The International Journal of Pharmaceutical Compounding **Compounding Formulation Contest**

Entry Deadline July 1, 1998

Winners will receive a complimentary two-year subscription to the *International Journal of Pharmaceutical Compounding*. Winning formulations with a brief bio of the author will be published in the *IJPC*.

Formulas should be original and relatively new. The judges will consider the following criteria:

1. Is the formula rational for intended use?
2. Are the components compatible, or, have any incompatibilities been corrected?
3. Is the formula intended to enhance patient compliance or to treat a difficult problem?
4. Is the formulation designed to enhance physical and chemical stability?
5. Is the formula unique? Can it be uniquely packaged and presented to the patient?

Please include the following information:

1. Formula name
2. Ingredients (including quantity and purpose in formula)
3. Use
4. Method of Preparation
5. Packaging
6. Labeling
7. Stability (if documented)
8. References/sources

And please include:

- Your name
- Your designation as pharmacist or student
- Address, city, state, country, and zip or postal code
- Phone numbers: work, home, fax

One RPh and one student will be awarded the prize and be published in the *Journal*. Nonwinning entries may also be considered for future publication in the *IJPC*.

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