



# Comparison of EMERPHED<sup>®</sup> (Ephedrine Sulfate) Injection with Current Concentrated Ephedrine Products in Simulated Clinical Settings

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**Abstract:** During surgical procedures, patients can have potentially life-threatening hypotension that requires immediate treatment with ephedrine sulfate, which requires compounding at the patient's bedside. This study was conducted to validate and compare Nexus Pharmaceutical's EMERPHED<sup>®</sup>, a pre-diluted ephedrine sulfate injection, with commercially used concentrated ephedrine sulfate in a simulated clinical setting. Twenty-four compounding simulations were performed in the clinical setting to simultaneously formulate EMERPHED<sup>®</sup> and concentrated ephedrine with a standardized dose of 10mg. The time to prepare the formulations, syringe volume, and the remaining contents of each vial were measured to determine compounding efficacy. Wastage reduction was theoretically discussed based on the waste disposal, and beyond use date. Inter-day variations were evaluated on different parameters. The time taken to formulate EMERPHED<sup>®</sup> was significantly faster ( $104.10 \pm 21.78$  vs  $70.63 \pm 12.45$  seconds) than concentrated ephedrine ( $P \leq 0.05$ ). The mean value for EMERPHED<sup>®</sup> was higher for the syringe accuracy, although it was not statistically significant ( $P = 0.20$ ) compared to concentrated ephedrine. Whereas for the remaining vial volume accuracy, EMERPHED<sup>®</sup> performed better ( $97.70 \pm 1.55\%$  Vs  $78.85 \pm 10.81\%$ ) than concentrated ephedrine ( $P \leq 0.05$ ). Participants improved in the time to formulate both products between the first and second day. There was no significant difference in the percent mean accuracy of syringe dosing and remaining vial volume between days. There was no detected difference in waste reduction. EMERPHED<sup>®</sup> showed significantly greater compounding efficacy and ease of use compared to commercially available concentrated ephedrine in the clinical simulations. The results indicate that EMERPHED<sup>®</sup> could be a potential replacement option to institutions using concentrated ephedrine.

**Keywords:** Clinical Simulation, Ephedrine, Compounding, Dose Accuracy, Error Reduction, EMERPHED<sup>®</sup>

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## 1. Introduction

Ephedrine sulfate is a prescription medicine used to treat the symptoms of low blood pressure (hypotension) due to an anesthetic being used in the operating room (OR) causing the patient to become hypotensive [1-4]. Ephedrine sulfate is often provided in either vials or ampules as a concentrated formulation requiring dilution for use. These concentrated formulations require multiple steps to administer which increases the risk for a medication administration error to

occur [5, 6]. One study reported that 48% of errors with IV medications occur during the preparation process or administration because of multiple required steps, syringe-to-syringe transfer, unnecessary dilution, and the use of saline flush syringes to dilute IV medications [7, 8]. Recently the FDA approved an alternative ephedrine sulfate formulation, EMERPHED<sup>®</sup>, which requires only 3 steps for administration and aligns with standardization recommendations for patient safety with Anesthesia Patient Safety Foundation (APSF), American Society of Health-

System Pharmacists (ASHP), and the Institution for Safe Medication Practices (ISMP) [9-12].

The objective of this study was to validate and compare Nexus Pharmaceutical's EMERPHED<sup>®</sup>, a pre-diluted ephedrine sulfate injection, with commercially used concentrated ephedrine sulfate in a simulated clinical setting. Concentrated ephedrine requires dilution at the patient's bedside, whereas EMERPHED<sup>®</sup> does not.

Compounding efficacy was evaluated by comparing compounding parameters between vials of commercially available concentrated ephedrine sulfate (50mg/mL), and EMERPHED<sup>®</sup> (5mg/mL) in a simulated OR setting. Concentrated ephedrine (50mg/mL) was used to prepare diluted ephedrine (5mg/mL) at bedside OR. Simulations were conducted in an OR setting using the Medical College of Wisconsin (MCW) Standardized Teaching Assessment Resource (STAR) center. EMERPHED<sup>®</sup> was compared with commercially available concentrated ephedrine sulfate and evaluated for the following parameters: ease of use, error reduction, and wastage reduction.

## 2. Materials/Methods

This study was conducted at MCW located in Milwaukee, WI. Investigators from MCW – School of Pharmacy and Froedtert Hospital (FH) teamed up to perform the simulations. The STAR Center provides a controlled environment where students, residents, physicians, nurses, and other healthcare professionals can practice their clinical skills using standardized (or actor) patients, medical simulators, and task trainers under the direction of MCW faculty and staff. In this study we have used a simulated OR environment. EMERPHED<sup>®</sup> was provided by Nexus Pharmaceuticals and commercially available concentrated ephedrine sulfate and other supplies were procured from MCW and FH. The study was approved by the MCW/FH Institutional Review Board (PRO00038758). Financial support and EMERPHED<sup>®</sup> were provided from Nexus Pharmaceuticals Inc.

### 2.1. Simulation Experiments

Vial volumes were calibrated before the experiment to remove measuring variances and were separated as the concentrated ephedrine group (group 1) and EMERPHED<sup>®</sup> group (group 2). Groups 1 and 2 were required to formulate a standardized dose of 10mg with a concentration of 5mg/mL. Group 1 had to withdraw the concentrated ephedrine from commercially available concentrated ephedrine in a syringe and dilute the product. Group 2 had to withdraw ephedrine from EMERPHED<sup>®</sup> (no dilution needed). Afterwards, each group turned towards the patient to deliver syringes to a healthcare professional to administer the medication at bedside. All the simulations were recorded (audio and video). Three key objectives were set to analyze the simulation.

### 2.2. Ease of Use (Reduction of Time)

Time was measured from the start of the experiment to the time taken to handover syringes to the healthcare professional. The noted time was used to calculate ease of use (reduction of time). Reduction of time was also evaluated through repetition in the event participants acquired better compounding abilities with more familiarity.

### 2.3. Error Reduction or Accuracy of Dosing

The vials were pre-calibrated to avoid variances in vial volumes due to potential manufacturer overfill. Filled syringes and any used vials at the pharmacy kiosk were collected by a third group (not connected with group 1 and 2) and their respective volumes were measured. The final volume was corrected for dilution and percent error was calculated.

*Wastage reduction:* Wastage reduction was calculated based on i) requirement of ephedrine in the OR ii) stability/Beyond Use Date (BUD) of the formulation, and iii) cost of disposal.

### 2.4. Clinical Setting

In the absence of a 5mg/mL preparation, FH clinicians must prepare concentrated ephedrine by withdrawing the entire contents (1mL) of a concentrated ephedrine 50mg/mL vial and then diluting to 10mL with normal saline in a 10mL syringe. Typically, 5-10mg (1-2mL) of this diluted ephedrine sulfate is given to a patient when needed. This syringe would then be available for that same patient if additional doses were needed. In many instances, only 10mg would be used for a patient instead of the entire 50mg. With consultation from FH clinicians in the OR setting, it was determined that a fixed dose of 10mg ephedrine sulfate would be used in the simulations. Concentrated ephedrine would require 0.2mL to be withdrawn from the concentrated ephedrine vial and then diluted to 2mL with normal saline. EMERPHED<sup>®</sup> does not require dilution, therefore, 2mL would be withdrawn directly. Multiple syringe sizes are used in the OR, but only 3mL syringes, with an accuracy down to 0.1mL, were used to prevent additional variations.

### 2.5. Pre-simulation Preparation

EMERPHED<sup>®</sup> and concentrated ephedrine is available as 10mL and 1mL vials respectively. Vial volumes required pre-calibration before the simulations due to concerns of drug overfill, approximately 10% of stated volume, during the manufacturing process. The contents of 26 concentrated ephedrine vials were emptied into a large beaker that was then covered with parafilm to prevent drug evaporation. The vials were dried out to ensure there was no product residue. A 1mL pyrogen-free serological pipette from Falcon® Brands was used to fill each vial with 1mL of the ephedrine that was stored. A new pipette was used for each vial. These pipettes were used because they have a measurement accuracy of 0.01mL and allowed for measurements of the vial contents after the simulations. The vials were resealed using a 13mm crimper that applied a new rubber stopper and

an aluminum flip off cap that hung off the vial neck (Figure 1). The same process was performed for 26 vials of EMERPHED<sup>®</sup> using the same 1mL pipettes but the vials were calibrated to 10mL. A new pipette was used for each vial. A 20mm crimper was used to reseal the EMERPHED<sup>®</sup> vials. The vial caps used on the EMERPHED<sup>®</sup> could be fully removed, unlike the concentrated ephedrine caps. The caps for the concentrated ephedrine and EMERPHED<sup>®</sup> were crimped with a blue cap instead of the yellow factory cap to prevent calibrated and non-calibrated vials from being mixed.



**Figure 1.** From left to right: empty concentrated ephedrine, fully sealed calibrated concentrated ephedrine, opened calibrated concentrated ephedrine vial.



**Figure 2.** Pictured left to right; drug kiosk tray, cart set up.

The drug supply kiosk trays were placed onto two carts which contained a sharps container and yellow dispensing tray on the second shelf (Figure 2). Each kiosk tray would be resupplied after each simulation. Participants had a marked fixed position to stand at during the simulation. Both locations were equidistant from the patient's bedside. Each station had one healthcare professional next to the bed that stood equidistant from the patient's bedside and from the participants to receive formulations after preparations. Pictures of room layout is provided in the online supplement as Appendix 1.

## 2.7. Participants

Personnel (OR pharmacists, faculty, students) from healthcare backgrounds were used for this study. The participants were educated about the compounding simulation activity and an information sheet was provided

All tasks were performed by the same individual, who conducted measurements of the drug products before and after the simulations. Two random vials for each formulation were picked the day before the first simulation to verify that all products were calibrated to their desired volumes. These vials were 100% accurate for their respective calibrated volumes.

## 2.6. Room Setting

Simulated drug kiosk trays were made with the help of FH clinicians. These kiosk trays were made with look-a-like-sound-a-like (LASA) medications along with other common OR drug kiosk medications (Figure 2). Both trays were made to be identical, with the only change being whether concentrated ephedrine or EMERPHED<sup>®</sup> were present. Each tray was comprised of two vials of each of the following: dexamethasone, esmolol, potassium chloride, calcium gluconate, multivitamin, two sets of phenylephrine, tranexamic acid, regular/NPH insulin, heparin, metoclopramide, ondansetron and either EMERPHED<sup>®</sup> or concentrated ephedrine. Each tray was supplied with four of the following: 3mL syringes, 18-gauge X 1 1/2" needles, alcohol wipes, and 10mL normal saline vials. The trays also contained tamper-proof syringe tops.

beforehand and is provided in the online supplement as Appendix 2. Before the study, it was assumed that the time to dispense the medication (compounding + dispensing) would fall from a mean time of 90 (SD=36) seconds to 30 (SD=12) seconds, statistical analysis required at least five simulations for concentrated ephedrine and EMERPHED<sup>®</sup> to achieve 80% power to detect a statistically significant results with an alpha of 0.05.

A pre-test run of the simulation was performed with the participants one week before the study. The personnel were provided instructions on how to prepare each formulation as well as the room set up to eliminate variation in the familiarity of the room design and how to formulate the products. Six participants agreed to participate, and two groups were created to run the simulation for concentrated ephedrine and EMERPHED<sup>®</sup> simultaneously. Although five

simulations (10 compounding activities) were required, we were able to conduct a total of 24 simulations (48 compounding activities), resulting in each participant performing a total of eight simulations in different sessions

(Table 1). Data sheet represents collection for participants A and B on day one (simulation 1-4) and day two (simulation 1-4). Similar tables were used for participants C-F.

*Table 1. Example Data Collection Sheet for Participants A and B.*

	Group 1	Participant designation	Time (sec)	Syringe volume (ml)	Remaining Vial Volume (mL)
Simulation 1	EMERPHED®	A1			
Simulation 2	Concentrated Ephedrine	A2			
Simulation 3	EMERPHED®	A3			
Simulation 4	Concentrated Ephedrine	A4			
Simulation 5	EMERPHED®	A5			
Simulation 6	Concentrated Ephedrine	A6			
Simulation 7	EMERPHED®	A7			
Simulation 8	Concentrated Ephedrine	A8			

*Table 1. Continued.*

	Group 2	Participant designation	Time (sec)	Syringe volume (ml)	Remaining Vial Volume (mL)
Simulation 1	Concentrated Ephedrine	B2			
Simulation 2	EMERPHED®	B1			
Simulation 3	Concentrated Ephedrine	B4			
Simulation 4	EMERPHED®	B3			
Simulation 5	Concentrated Ephedrine	B6			
Simulation 6	EMERPHED®	B5			
Simulation 7	Concentrated Ephedrine	B8			
Simulation 8	EMERPHED®	B7			

All six participants were identified as a letter from A-F. These participants were then separated into the two groups. Group one consisted of participants A, C, and E, while group two consisted of participants B, D, and F. One member from each group was paired to another member from the other group and would always do simulations with the same participant to minimize variations. Group one would first make EMERPHED® then switch to make concentrated ephedrine, and group two would start by making concentrated ephedrine then switch to make EMERPHED®. Each pair of participants would do two rotations making the two formulations, allowing them to make EMERPHED® and concentrated ephedrine twice in one session. Two sessions were conducted each day. This allowed for a total of four simulations to be performed by the participants on each day and resulted in a total of 12 simulations (24 compounding activities) each day with all the paired participants. The participants were asked to return on a separate day to repeat the same simulations allowing for inter-day variations to be assessed and allowed for a total of 24 simulations (48 compounding activities) between the two days. The STAR Center recorded the encounters and the copies of all the recordings are with the PI of this study.

## 2.8. Simulation

Participants and carts were placed in a marked position so that they could not see each other's compounding activity. The simulation began when the STAR Center's intercoms asked for 10mg of ephedrine to be formulated. After the announcement, the healthcare professional on both sides of the room would start their stopwatch to measure the

time to formulate either product. After formulating their product, the participants were asked to place a tamper-proof syringe cap onto their formulation to prevent potential product loss.

Participants placed their final formulations and used vials into the yellow dispensing trays provided (Figure 2) and presented the tray to the healthcare professional. Their time would stop, and this would be the time to make the formulation. Notes were taken throughout simulations by the lead investigators. One factor that was noted was the time it took to remove the vial tops. The time it took to open the vials was recorded and subtracted from the overall time to formulate because both tops had to be removed differently. All the drug vials and syringes were placed into pre-marked bags that were labeled with the letter of the participant formulating, the product formulated, and a number to specify the simulation. All EMERPHED® bags were labeled with odd numbers, and all concentrated ephedrine bags were labeled with even numbers to prevent different formulated drugs being mixed. These bags were collected, and their contents were evaluated after all simulations had been performed. The contents of the syringes, and vials were measured by the same person who pre-calibrated the vials.

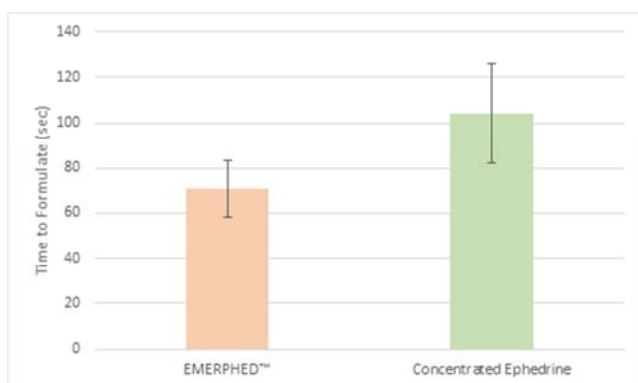
After the study was completed, participants were debriefed on the scenarios to evaluate their thoughts on the different formulations via a Qualtrics™ survey. This survey asked about their level of skill and length of formulating experience. The questions asked evaluated the participant's view on the three objectives of ease of use, accuracy of dosing, and waste reduction, and is provided in the online supplement as Appendix 3.

### 3. Results and Discussion

EMERPHED<sup>®</sup> and commercially available concentrated ephedrine formulations were compared for the compounding efficacy in the simulated clinical setting. The compounding efficacy was measured for error reduction, and ease of use. Wastage reduction was theoretically discussed based on the waste disposal, BUD, and cost of the formulation. A two-tail t-test was used for statistical analysis.

#### 3.1. Ease of Use [Time to Formulate]

The time to formulate 10mg of EMERPHED<sup>®</sup> was  $70.63 \pm 12.45$  seconds compared to  $104.10 \pm 21.78$  seconds with concentrated ephedrine. EMERPHED<sup>®</sup> was formulated faster than concentrated ephedrine by  $33.47 \pm 19.47$  seconds (Figure 3). Ephedrine showed a larger standard deviation (SDs), when compared to EMERPHED<sup>®</sup>. This shows there is more variation in time to formulate concentrated ephedrine, while EMERPHED<sup>®</sup> is more consistent. This is more impactful when considering the level of experience of the participants. All participants had less than six months of parenteral compounding experience but were able to consistently make EMERPHED<sup>®</sup>. Ephedrine not only takes longer to make but has not shown consistent formulating time.



**Figure 3.** Ease of use (reduction in time) for each formulation measured in seconds to formulate ( $n=24$ ,  $p \leq 0.05$ ).

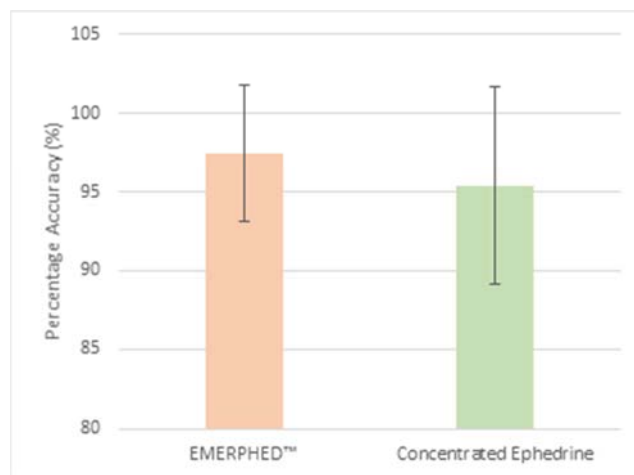
#### 3.2. Error Reduction or Accuracy of Dosing

Accuracy of dosing was evaluated by measuring the syringe volume prepared for both ephedrine sulfate formulations. The remaining volume left in the vial was also measured to double check the dosing accuracy. Syringe volumes and remaining vial volumes are used to evaluate the accuracy of dosing.

##### 3.2.1. Accuracy of Syringe Dosing

EMERPHED<sup>®</sup> showed an accuracy of  $97.50 \pm 4.33\%$  compared to  $95.42 \pm 6.28\%$  with concentrated ephedrine (Figure 4). Although the mean value for EMERPHED<sup>®</sup> is higher for the syringe accuracy, it is not statistically significant ( $P=0.20$ ) compared to concentrated ephedrine due to the large SD values. In some instances, participants formulated products with more than 2mL causing the accuracy to become skewed and greater than 100%. The data

was manually modified to show the correct percent accuracy. This kind of dose discrepancy would have a larger impact with the concentrated ephedrine as it needs dilution, whereas clinicians can easily adjust the volume of the EMERPHED<sup>®</sup> to correct for a dosing error.



**Figure 4.** Final syringe volume measured as % accuracy of syringe dosing ( $n=24$ ,  $p=0.20$ ).

The SD of concentrated ephedrine was larger than that of EMERPHED<sup>®</sup> for accuracy of syringe dosing. In the case of concentrated ephedrine, negative vial pressure would cause difficulty in vial manipulation when the concentrated ephedrine syringe was inserted in the normal saline vial. It was noticed that some volume may have been lost inside the normal saline vial, leading to inaccurate concentrated ephedrine dosing. These kinds of incidents result in delays in the time to administration and could cause improper dosing if it is not noticed. EMERPHED<sup>®</sup> has a larger vial size and can withstand much greater levels of pressure while formulating the product, avoiding these concerns.

##### 3.2.2. Accuracy of Remaining Vial Volume

After the syringe was prepared, the remaining volume in the vial was measured and percent accuracy of the remaining vial volume was calculated based on the theoretical volume in the vial. The predicted remaining volume for EMERPHED<sup>®</sup> was 8mL, and the predicted remaining volume for concentrated ephedrine was 0.8mL. EMERPHED<sup>®</sup> showed a significantly higher accuracy of  $97.70 \pm 1.55\%$  compared with  $78.85 \pm 10.81\%$  for concentrated ephedrine ( $P < 0.05$ ) for their respective predicted remaining vial volume (Figure 5). The contributing factors that caused concentrated ephedrine's accuracy to be substantially lower than EMERPHED<sup>®</sup> could be the small volumes (0.2mL) needed to withdraw from the stock 50mg/mL vial and air bubbles. The ability to balance the pressure in EMERPHED<sup>®</sup>, due to its larger vial size, helped to minimize the product loss and is supported by the small SD, compared to the large SD value of concentrated ephedrine.



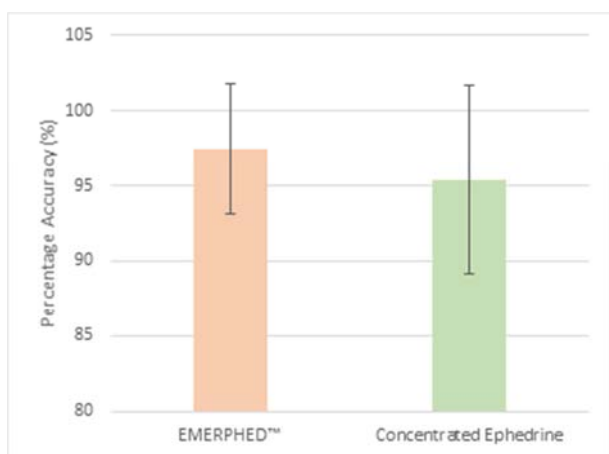


Figure 5. Final remaining vial volume in % accuracy ( $n=24$ ,  $p \leq 0.05$ ).

### 3.3. Inter-Day Variations

Inter day variations were observed for each of the compounding parameters: i) Each formulation was evaluated for inter-day variations and ii) both formulations were compared within the same day. (Table 2).

Participants improved in the time to formulate ( $P < 0.05$ ) for both products between the first and second day (Figure 6). Although EMERPHED® had a small variation between the two days, it was relatively consistent between days. We have observed that the performance of EMERPHED® was significantly greater ( $P < 0.05$ ) in both days (Table 2). This

can be attributed to the ready to use nature of the EMERPHED® allowing compounders to consistently produce the formulation. Ephedrine may require more training to properly formulate, and there would be less consistency in the time to formulate even with familiarity with the formulation. With practice individuals can improve the time to formulate either product, but EMERPHED® shows consistent results regardless of the level of someone's compounding experience or their familiarity with the product.

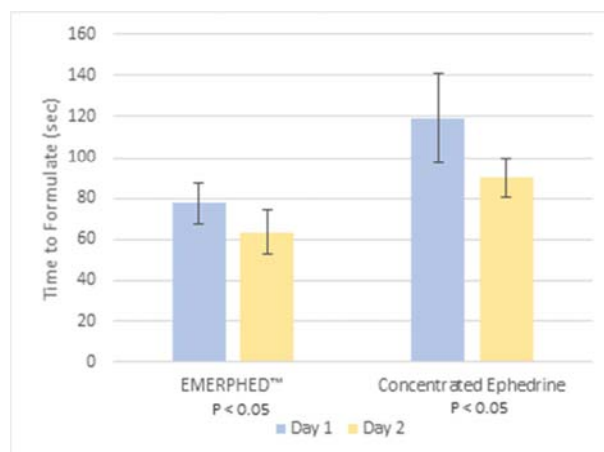


Figure 6. Inter-day variation for the ease of use (reduction in time) of EMERPHED® and concentrated ephedrine ( $n=12$ ). P-values for each formulation comparing day 1 to day 2 performance.

Table 2. Variations Between EMERPHED® and Concentrated Ephedrine Between Days P-values are listed for each day comparing each individual measure for both formulations.

	Day 1 ( $n=12$ for each formulation)		Day 2 ( $n=12$ for each formulation)	
	EMERPHED® Samples	Concentrated Ephedrine Samples	EMERPHED® Samples	Concentrated Ephedrine Samples
Time to formulate (seconds±SD)	77.61±9.91 $P \leq 0.05$	117.86±21.85	63.64±6.05 $P \leq 0.05$	90.33±9.63
Accuracy of syringe dosing (%±SD)	95.83±5.34 $P=0.88$	95.42±6.91	99.17±1.86 $P \leq 0.05$	95.42±5.57
Accuracy of remaining vial volume (%±SD)	97.50±1.30 $P \leq 0.05$	78.54±11.67	97.90±1.75 $P \leq 0.05$	79.17±9.87

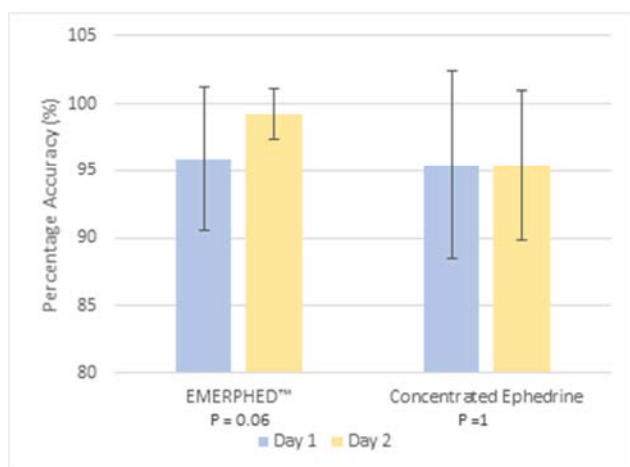


Figure 7. Inter-day variations in the percent accuracy of the formulated syringes ( $n=12$ ). P-values for each formulation comparing day 1 to day 2 performance.

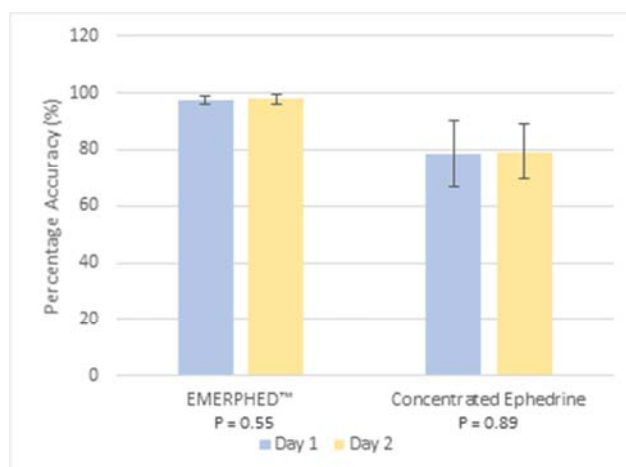


Figure 8. Inter-day variations in the accuracy of the remaining vial volume ( $n=12$ ). P-values for each formulation comparing day 1 to day 2 performance.

The percentage mean accuracy of the formulated dose (syringe) of EMERPHED<sup>®</sup> increased from day one to day two, although the difference was not significant ( $P=0.06$ ). We have noted that SD on day two was much smaller compared to day 1 (Figure 7). Ephedrine had a minimal change between each day and was near identical in terms of the standard deviation and having a P-value of 1. The SD of concentrated ephedrine was larger on both days compared to EMERPHED<sup>®</sup>.

Further evaluating the data, we have observed that there was no significant difference ( $P=0.88$ ) between both formulations on day 1, whereas a significant difference was observed on day 2 ( $P < 0.05$ ) (Table 2). This implies that the performance of the participants improved between days, most notably in EMERPHED<sup>®</sup>. This is the result of the participants having increased familiarity of the product and an improvement in their compounding technique. This data indicates that EMERPHED<sup>®</sup> was easier to manipulate compared to the concentrated ephedrine when formulating.

There was no significant difference in the remaining vial volume seen in either formulation between the two days (Figure 8). However, the standard deviation present in concentrated ephedrine was far larger than that of EMERPHED<sup>®</sup> on each day. Moreover, EMERPHED<sup>®</sup> showed higher remaining vial volume accuracy on both days compared to concentrated ephedrine ( $P < 0.05$ ) (Table 2).

### 3.4. Waste Reduction

In practice concentrated ephedrine 1mL vial (50mg/mL) is diluted to 10mL with normal saline for use in the OR setting, whereas EMERPHED<sup>®</sup> (5mg/mL) comes in a 10mL ready to use vial. Both products are one-time use vials and would only be used for one patient. Moreover, the unused drug would be discarded in both cases. If any drug is left over, the vial would be disposed in a drug disposal bin, and if no drug is left in the vial, then the vial would be placed in the normal trash. It has been observed that both products have the same beyond use date of 24 months as per the manufacturer's information [13, 14]. Both EMERPHED<sup>®</sup> and concentrated ephedrine has an acquisition cost of \$20 per vial directly from the manufacturer [15]. Based on the above-mentioned information, we did not envisage any difference in the cost of waste disposal. We did not observe any mix-ups with any LASA drugs in the simulations.

### 3.5. Participant Survey

All participants responded to the post study survey and provided feedback on their experiences formulating the two products in the simulations (Appendix 3). Four of the six participants reported 0-3 months of parenteral compounding experience, while the remaining two reported 3-6 months of experience. Four individuals identified themselves as beginner level parenteral compounders, and the other two identified as having a moderate level of experience. Participants stated they would anticipate a significant reduction in waste with EMERPHED<sup>®</sup> compared to

concentrated ephedrine. All six participants stated that they felt the ease of use (reduction of time) to be enhanced with EMERPHED<sup>®</sup>, that they would anticipate EMERPHED<sup>®</sup> to have better dosing accuracy, and that they would recommend hospitals to switch from concentrated ephedrine to EMERPHED<sup>®</sup>.

## 4. Conclusions

EMERPHED<sup>®</sup> showed significantly greater ease of use and compounding efficacy compared to the commercially available concentrated ephedrine in the clinical simulations. EMERPHED<sup>®</sup> takes less time to formulate compared to concentrated ephedrine. The accuracy of dosing was measured based on i) syringe volume and ii) remaining vial volume. The percentage mean accuracy with the syringe volume was higher for EMERPHED<sup>®</sup>, however it was not significantly different than concentrated ephedrine. On the contrary, EMERPHED<sup>®</sup> showed better percentage mean accuracy compared to concentrated ephedrine for the remaining vial volume. This indicates that EMERPHED<sup>®</sup> may produce less errors in formulating the final desired volume. EMERPHED<sup>®</sup> and concentrated ephedrine was found to be identical regarding the waste reduction. All the participants agreed that hospitals should consider switching from concentrated ephedrine to EMERPHED<sup>®</sup> as per the post-study Qualtrics survey. These results indicate that depending upon the hospital demand, EMERPHED<sup>®</sup> could be a replacement option to institutions using concentrated ephedrine without adding an additional cost to the institution.

To the best of our knowledge, this is the first attempt to combine a sterile compounding lab and a clinical simulation setting to compare different commercially available pharmaceutical products. In the future, we will use the combination of clinical simulation settings and the sterile compounding lab environment to assess the compounding efficacy of various pharmaceutical formulations. The outcome of these studies would be beneficial to those in the healthcare setting when evaluating various pharmaceutical products without causing a risk to patients while being cost effective.

## Conflict of Interest

The authors declare that they have no competing interests.

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## Appendix

### Appendix 1. Room Design



**Figure 9.** EMERPHED® room layout.



**Figure 10.** Ephedrine room layout.

### Appendix 2. Informational Sheet

Comparison of Nexus Pharmaceuticals Products with Commercially Used Products in Simulated Clinical Settings

You are receiving this survey to participate in a research study to validate and compare Nexus Pharmaceuticals

products with commercially used products in simulated sterile product production and clinical settings. Nexus pharmaceuticals is offering Nexus EMERPHED® 5mg/mL, a ready to use formulation, as an alternative to ephedrine 50mg/mL which is currently used in the hospital setting. Simulation of the Nexus product use in the operating room setting will be performed using the STAR center and Sterile Products Lab. EMERPHED® will be compared with a commercially available ephedrine sulfate injection and evaluated for the following parameters (In the order of preference):

1. Error Reduction or Accuracy of dosing
2. Wastage reduction
3. Ease of use (reduction of time) and Time to administer formulation

Students will compound ephedrine formulations at the STAR center. Anyone with compounding expertise can participate in this study. This study will be done in 2-3 days at different time period. Participants will be asked to participate in 5 total simulations over the 2-3 days. Taking part in this research is not part of your job duties nor any requirements and refusing will not affect your educational outcome. You will not be offered nor receive any special credits if you take part in this research.

Although you will not get personal benefit from taking part in this research study, your responses may help us understand more about the perceived barriers toward completing original research. We will encourage you to take part in a post-study debrief survey. Of course, you have a choice about whether or not to complete the questionnaire and survey, but if you do participate, you are free to skip any questions or discontinue at any time. The survey will take about 5 to 10 minutes to complete. Simulations will be recorded but will not be distributed to the public. Data collected will be distributed to the sponsor and may be used for publications or presentations. If you are not comfortable with being videotaped, then contact the study principle investigator.

Your response to the survey will be kept confidential to the extent allowed by law. When we write about the study you will not be identified, and your name will not be used in presentations or publications. If you have questions about the study, please feel free to ask; our contact information is given below. If you have questions about your rights as a research participant or want to report any problems or complaints, you can call the Medical College of Wisconsin / Froedtert Hospital Research Subject Advocate at (414) 955-8844.

By completing the questionnaire and survey, you are consenting to participate in this research project. This project, "Comparison of Nexus Pharmaceuticals Products with commercially used products in simulated clinical settings," has been reviewed and approved by the Medical College of Wisconsin / Froedtert Hospital Institutional Review Board (IRB).

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### Appendix 3. Nexus Debrief Survey

Q1 - How much experience you have in compounding parental formulations?

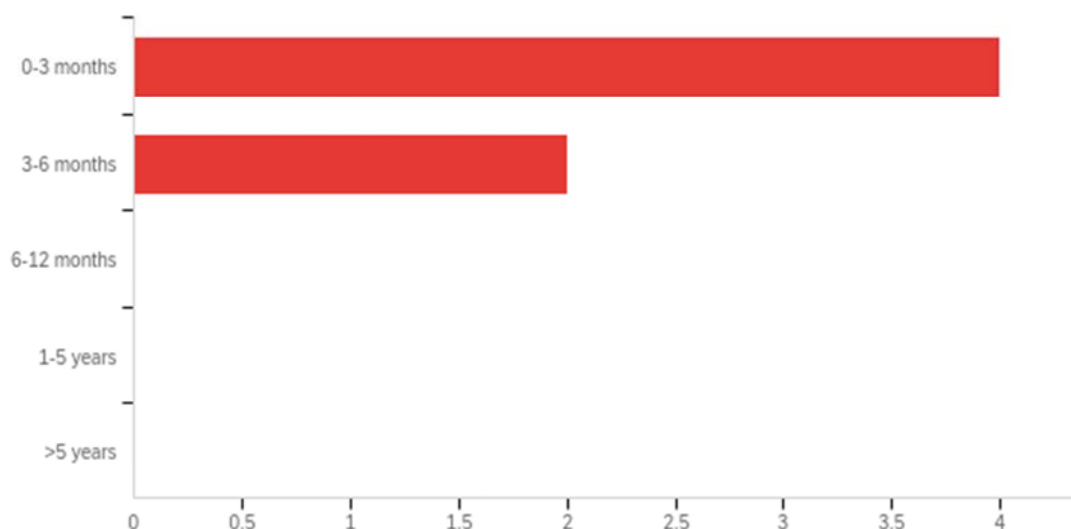


Figure 11. Quadratics graphical response to survey question 1. Multiple choice response.

Table 3. Participant responses to survey question 1. Multiple choice response.

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
How much experience you have in compounding parental formulations?	1.00	2.00	1.33	0.47	0.22	6

#	Answer	%	Count
1	0-3 months	66.67%	4
2	3-6 months	33.33%	2
3	6-12 months	0.00%	0
4	1-5 years	0.00%	0
5	>5 years	0.00%	0
	Total	100%	6

Q2 - Rate your level of experience preparing parental formulations.

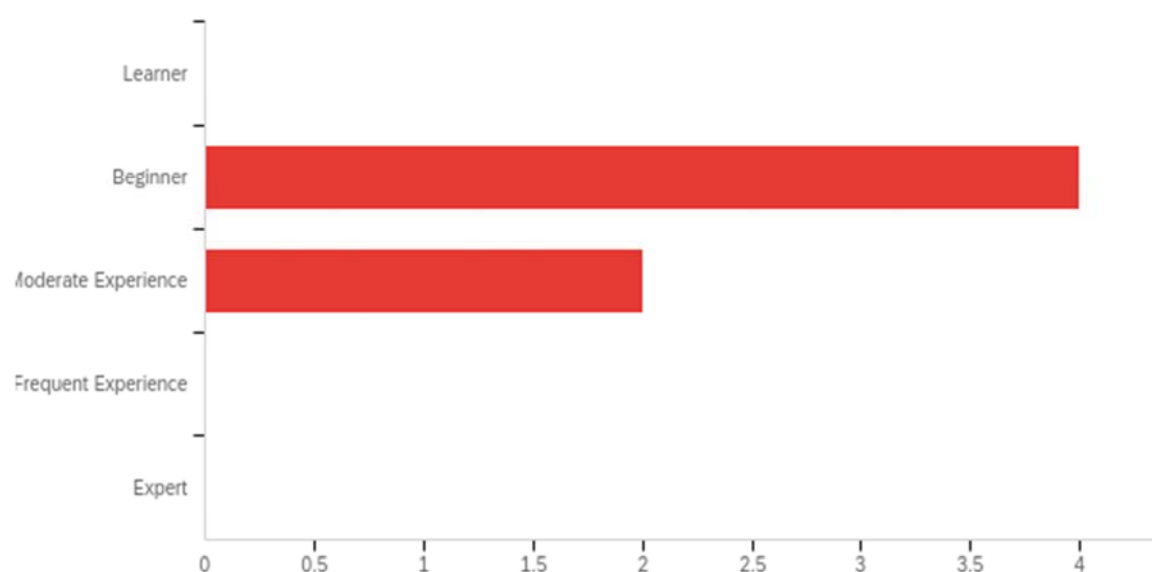


Figure 12. Quadratics graphical response to survey question 2. Multiple choice response.

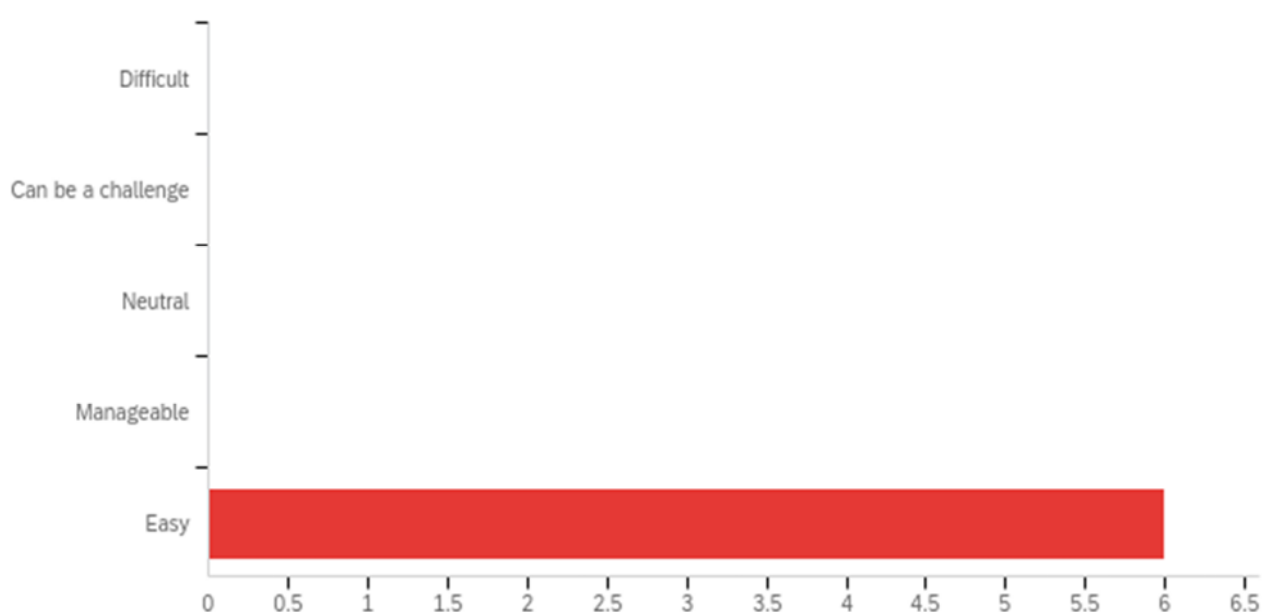
**Table 4.** Participant responses to survey question 2. Multiple choice response.

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Rate your level of experience preparing parental formulations.	2.00	3.00	2.33	0.47	0.22	6

#	Answer	%	Count
1	Learner	0.00%	0
2	Beginner	66.67%	4
3	Moderate Experience	33.33%	2
4	Frequent Experience	0.00%	0
5	Expert	0.00%	0
	Total	100%	6

Q3 - How would you rate the ease of use (or reduction of time) to compound EMERPHED® 5mg/mL compared to ephedrine 50mg/mL?

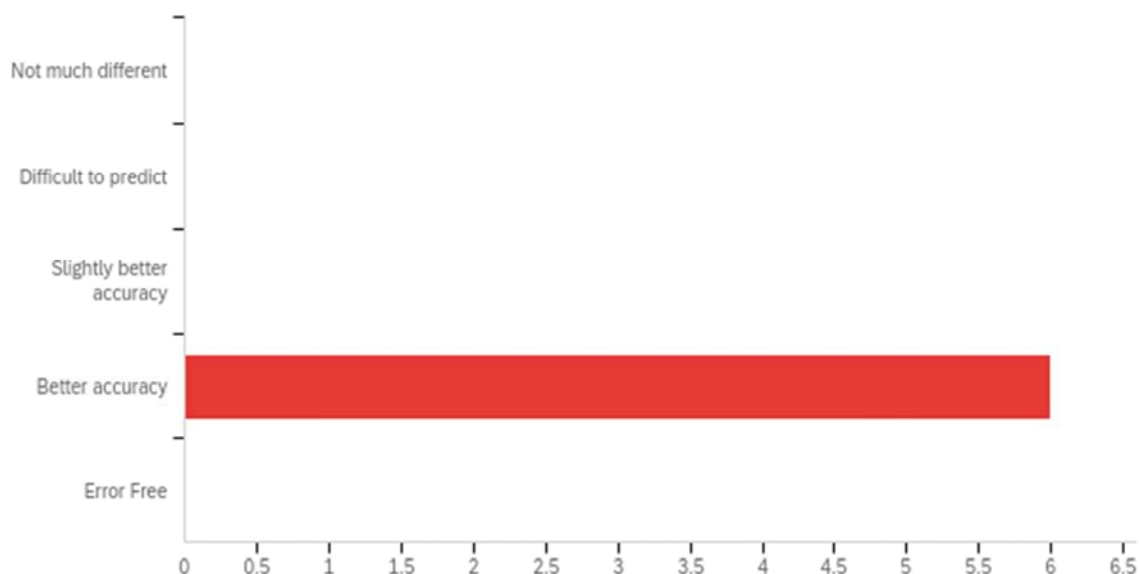
**Figure 13.** Quadratics graphical response to survey question 3. Multiple choice response.**Table 5.** Participant responses to survey question 3. Multiple choice response.

#	Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
1	How would you rate the ease of use (or reduction of time) to compound EMERPHED® 5mg/mL compared to ephedrine 50mg/mL?	5.00	5.00	5.00	0.00	0.00	6

#	Answer	%	Count
1	Difficult	0.00%	0
2	Can be a challenge	0.00%	0
3	Neutral	0.00%	0
4	Manageable	0.00%	0
5	Easy	100.00%	6
	Total	100%	6

Q4 - How would you anticipate the accuracy of dosing (or Error Reduction) for EMERPHED® 5mg/mL compared to ephedrine 50mg/mL?



**Figure 14.** Quadratics graphical response to survey question 4. Multiple choice response.

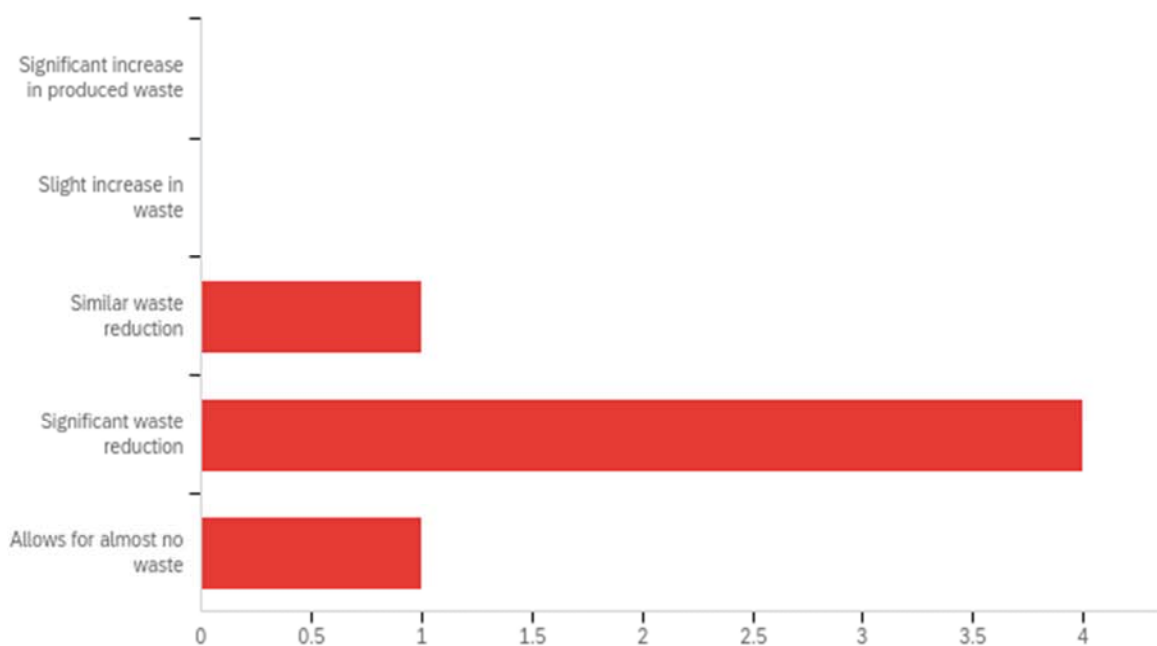
**Table 6.** Participant responses to survey question 4. Multiple choice response.

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
How would you anticipate the accuracy of dosing (or Error Reduction) for EMERPHED <sup>®</sup> 5mg/mL compared to ephedrine 50mg/mL?	4.00	4.00	4.00	0.00	0.00	6

#	Answer	%	Count
1	Not much different	0.00%	0
2	Difficult to predict	0.00%	0
3	Slightly better accuracy	0.00%	0
4	Better accuracy	100.00%	6
5	Error Free	0.00%	0
	Total	100%	6

Q5 - How would you anticipate the ability to reduce waste when using EMERPHED<sup>®</sup> 5mg/mL vs ephedrine 50mg/mL?



**Figure 15.** Quadratics graphical response to survey question 5. Multiple choice response.

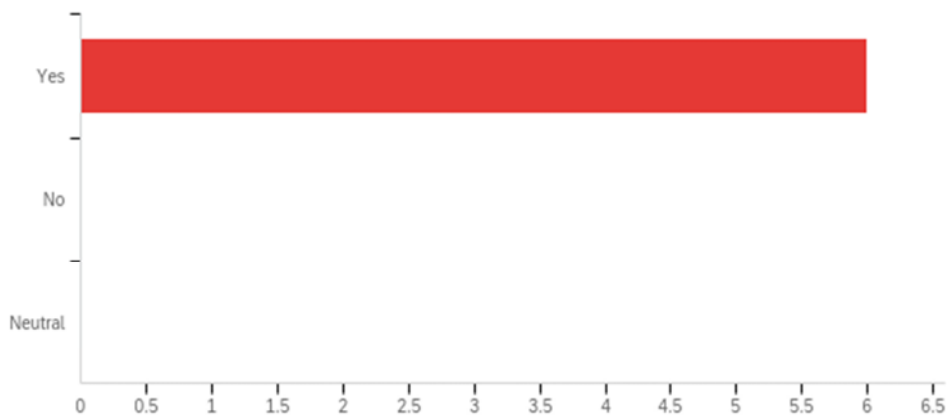
**Table 7.** Participant responses to survey question 5. Multiple choice response.

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
How would you anticipate the ability to reduce waste when using EMERPHED® 5mg/mL vs ephedrine 50mg/mL?	3.00	5.00	4.00	0.58	0.33	6

#	Answer	%	Count
1	Significant increase in produced waste	0.00%	0
2	Slight increase in waste	0.00%	0
3	Similar waste reduction	16.67%	1
4	Significant waste reduction	66.67%	4
5	Allows for almost no waste	16.67%	1
	Total	100%	6

Q6 - Would you recommend hospitals switch from ephedrine 50mg/mL to EMERPHED® 5mg/mL?

**Figure 16.** Quadratics graphical response to survey question 6. Multiple choice response.**Table 8.** Participant responses to survey question 6. Multiple choice response.

Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
Would you recommend hospitals switch from ephedrine 50mg/mL to EMERPHED® 5mg/mL?	1.00	1.00	1.00	0.00	0.00	6

#	Answer	%	Count
1	Yes	100.00%	6
2	No	0.00%	0
3	Neutral	0.00%	0
	Total	100%	6

Q7 - Please describe any additional comments you have on your experience with this compounding simulation.

**Table 9.** Participant responses to survey question 7. Free response.

Please describe any additional comments you have on your experience with this compounding simulation.
There were many more opportunities for error with the ephedrine 50mg/ml. For example: incorrect concentration in syringe, ephedrine contaminates saline leading to higher concentration in next dose, saline contaminates the ephedrine leading to a decreased concentration for the next dose, or an increased risk of corks in the syringe.
Compounding ephedrine took a lot longer than Emerphed and was more difficult to get appropriate volumes.
It was easier to draw up the Emerphed in terms of use and time. I also thought the ephedrine vial was hard to open. It was also easier just drawing up the Emerphed, whereas, for the ephedrine, it had to be diluted with sterile water.

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