Accuracy Evaluation of the Diana™ Hazardous Drug Compounding System
Validations Technologies, Incorporated, San Diego, CA

BACKGROUND
The Diana hazardous drug compounding system, manufactured by ICU Medical Inc., is the world’s first needlefree user-controlled automated sterile compounding system for the accurate, safe, and efficient preparation and reconstitution of hazardous drugs. The Diana system was designed to keep patients and clinicians safe from hazardous drug exposure during chemotherapy preparation and may also keep the drugs themselves safe from exposure to outside contaminants thanks to a microbiologically and mechanically closed design that protects the patient preparation from exposure to environmental contaminants while protecting the clinician from both exposure to the drug and accidental needlesticks.

ABSTRACT
To validate the accuracy of the Diana system, a series of laboratory studies was performed by an independent ISO-certified validation firm (Validation Technologies, San Diego, CA). These studies included recreating a variety of use conditions across a range of programmed volumes to confirm that the system’s fluid dispensing accuracy was within the manufacturer’s stated accuracy claim of <3% error for volume measurements. Results of the study confirm the manufacturer’s accuracy claims and verify that the Diana system is a reliable and repeatable fluid volume measurement and dispensing system. Additionally, it was observed that ≤1% error was consistently achieved at volumes ≥1 mL for channel one and volumes ≥5 mL for channel two when preparation sets and connected closed system components are manually primed before compounding.

INTRODUCTION
The process of measuring medication and diluent volumes during the compounding of intravenous medications has a number of inherent variables. For example, the standard allowed variation in manufactured pharmaceuticals and compounded preparations is 90% to 110% of the active ingredient. Syringe volume graduation markers have been shown to vary by up to ±5%. Human precision in reading the syringe sub-marking measurement is generally considered to be ≥ ±1 mL for fluid volumes drawn in syringe capacity ≥ 20 mL. And, finally, manufacturer diluent IV bags are not consistently overfilled, and the overfill varies between the lot numbers of the manufactured products.

As a result, the final compounded preparation can inadvertently be “out of specification” and not meet the required standards. These variations may also contribute to an admixture that differs from the physician-ordered prescription, potentially affecting small therapeutic window situations or contributing to unnecessary drug waste. Additional human factors such as interruptions, fatigue, and memory lapse are recognized in clinical literature to further contribute to preparation errors. The Diana hazardous drug compounding system helps take the variation out of manual drug preparation practice to create an accurate, reliable, and repeatable sterile preparation and safe handling process.

SYSTEM OVERVIEW
The Diana system is a user-controlled automated compounding system with two syringe pumps (dual channels) that are controlled by two high-precision step motors to facilitate small- and large-volume medication and diluent transfers. The system uses ICU Medical’s proprietary closed system, fluid-transfer components to help reduce exposure to hazardous drugs while preserving the sterility of the patient preparation.
Channel one uses a 20 mL syringe and cassette device with an integrated double-valve flow chamber technology system featuring two Spiros\textsuperscript{®} needlefree closed male luers to facilitate drug transfer between the drug manufacturer’s vial and the IV bag (or other male luer device connected to the patient IV container). Channel one is mainly used to add hazardous drugs to a patient container (IV bag, syringe, elastomeric pump) or for small-volume fluid transfers.

Channel two is mainly used for transferring diluents, filling elastomeric pumps, reconstituting lyophilized drugs, filling a series of syringes, or performing large-volume fluid transfers. Channel two uses a 50 mL syringe and a dedicated preparation set with a bonded Spiros closed male luer.

Both channels are controlled through an intuitive touch screen interface. Diana guides the operator through drug preparation and upon completion of each preparation. After each mix is completed, the Diana system sends the medication name, volume, time, and date to a printer that creates a label containing preparation information to complement validation and quality assurance process and help prevent medication errors. As a result, pharmacist review and quality checking of the patient preparation can be based on actual documentation created as a byproduct of automation rather than visual inspection of vials and syringes used by the operator.

MATERIALS AND METHODS
Accuracy validation tests were conducted using the Diana system and preparation sets along with ICU Medical’s closed system vial adapters and bag spikes componentry affixed to a standard IV bag container (see Table 1). The study was designed to test a range of programmed volumes and use-case conditions. The use-case conditions included new, pre-primed (manually primed) cassettes and diluent sets; new, non-pre-primed or machine-primed sets; and non-pre-primed, used cassettes and adapters. All tests were performed using normal speed on the device.

The tests were conducted using 0.9% sodium chloride, and the receiving bag was weighed before and after each programmed volume was transferred, with the difference in weight (grams) of each sample recorded. The weight was converted to volume in each case by using the following calculation: measured weight ÷ 1.0046 g/mL (the specific gravity of 0.9% sodium chloride).\textsuperscript{9} The percent error between the programmed (desired) volume and the measured (calculated) volume was calculated using the following formula: calculated volume – programmed volume ÷ programmed volume x 100 (all volumes in mL).

The scale used to weigh each measurement was tested for accuracy using standard gram weights across a range of weights (1, 20, 50, and 100 grams) and was found to be accurate to ±0.2% error.

TABLE 1: MATERIALS USED IN THE STUDY

<table>
<thead>
<tr>
<th>Product</th>
<th>Model Number</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diana System</td>
<td>CH5000</td>
<td>ICU Medical</td>
</tr>
<tr>
<td>Diana Cassette</td>
<td>CH4000 (Channel 1)</td>
<td>ICU Medical</td>
</tr>
<tr>
<td>Diana Diluent Set</td>
<td>CH4001 (Channel 2)</td>
<td>ICU Medical</td>
</tr>
<tr>
<td>ChemoClave Vial Adapter</td>
<td>CH-74</td>
<td>ICU Medical</td>
</tr>
<tr>
<td>Bag Spike</td>
<td>CH-10</td>
<td>ICU Medical</td>
</tr>
<tr>
<td>0.9% Sodium Chloride, 50 mL Bag (empty)</td>
<td>0409-7984-36</td>
<td>Hospira</td>
</tr>
<tr>
<td>0.9% Sodium Chloride, 500 mL Bag</td>
<td>0409-7983-30</td>
<td>Hospira</td>
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<tr>
<td>0.9% Sodium Chloride, 50 mL Vial</td>
<td>0409-4888-50</td>
<td>Hospira</td>
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<tr>
<td>Electronic Balance (0.000 g)</td>
<td>H1-4105</td>
<td>Setra</td>
</tr>
<tr>
<td>Diana System Printer</td>
<td>CH5100</td>
<td>Zebra</td>
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</tbody>
</table>
RESULTS

Scenario 1 tested manual priming of channel one cassette and vial adapter then dispensing at volumes of 1, 2, 5, 10, 20, 50, and 100 mL using 0.9% sodium chloride on channel one. Each volume tested was sampled 10 times, and a total of 100 data points were collected and analyzed. The average observed error ranged from -0.4% to 0.1% across the entire data set. The min-max error range observed from all measurements ranged from -1.0% to 0.6% over the 100 samples collected.

Scenario 2 tested manual priming of a diluent set then dispensing at volumes of 5, 25, 50, 100, and 250 mL using 0.9% sodium chloride on channel two. Each volume tested was sampled 10 times, and a total of 100 data points were collected and analyzed. The average observed error ranged from -0.5% to 0.1% across the entire data set. The min-max error range observed from all measurements ranged from 0.2% to 1.0% over the 100 samples collected.
Scenario 3 tested Diana priming of a new cassette and new vial adapter and dispensing accuracy of 0.9% sodium chloride at volumes of 1, 2, and 5 mL on channel one. The average observed error ranged from -1.9% to 1.8% across the entire volume range sampled. The min-max error range observed from all measurements ranged from 5.3% to 8.7% across the entire data set collection. Samples above 5 mL were not tested, as percent error would be more pronounced at smaller dispensed volumes as a result of a cassette or vial adapter priming volume error.

Channel two is designed to be manually-primed only; no machine-primed study was performed.

CONCLUSION
The greatest accuracy and precision was achieved with manual priming of a new cassette or diluent set, whereby error ≤1% was consistently achieved across all tested volumes. Less than 3% error was also achieved for volumes ≥2 mL when a new cassette and spike were machine-primed on channel one. Based on this study data, the Diana system channels one and two met the manufacturer’s accuracy claims. Additionally, the Diana system consistently met the manufacturer’s accuracy claims under the use-case conditions tested and exceeded manufacturer’s accuracy claims in all use-cases with large-volume transfers.

While this study was largely focused on measuring accuracy using 0.9% sodium chloride, a few tests using a 50/50 castor oil and ethanol solution—a surrogate for the viscous drug Paclitaxel—were conducted. The preliminary findings suggest comparable findings as shown above: no notable impact from use of a viscous solution was observed at normal speed. More study is needed to further investigate machine priming with a viscous fluid or impact of various syringe draw speed settings, particularly on channel one where various drug types may be frequently used.

References
1. http://www.pharmacopeia.cn/v29240/usp29nf24s0_c795.html