Received: 20 September 2018 | Revised: 28 December 2018 | Accepted: 10 January 2019

DOI: 10.1111/jcpt.12810

ORIGINAL ARTICLE

WILEY Journal of Clinical Pharmacy and Therapeutics

Female low dose tip syringes-increased complexity of use may compromise dosing accuracy in paediatric patients

Keliana O'Mara Pharm D[1] | Sarah Jane Gattoline Pharm D[2] | Christopher T. Campbell PharmD, BCPPS[1,3]

[1]Department of Pharmacy, UF Health Shands Children's Hospital, Newberry, Florida

[2]Pharmacy, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[3]University of Florida College of Pharmacy, Gainesville, Florida

Correspondence
Keliana O'Mara, Department of Pharmacy, UF Health Shands, Gainesville, FL.
Email: keliana.omara@gmail.com

Summary

What is known and objective: The International Organization for Standardization (ISO) created enteral device specifications to reduce tubing misconnections. The Global Enteral Device Supplier Association (GEDSA) supports a female design: standard and low dose tip (LDT). Concerns include increased complexity of use with adapters, dosing accuracy and workflow. No peer-reviewed studies have evaluated dosing accuracy of the complete female system with adapters. The objective of this study was to compare dosing accuracy of the female design to legacy syringes.

Methods: An in vitro study was conducted at the University of Florida College of Pharmacy pharmaceutics laboratory. Assessments were completed for syringe size, dispense methods and volumes, and adapters when applicable. A gravimetric scale and specific gravity were used to calculate administration volumes. The primary outcome was frequency administration volume exceeded 10% expected amount.

Results and discussion: A total of 576 tests were performed. The LDT resulted in significantly higher rates of unacceptable dosing variance compared to legacy (21.2% vs 7.4%, $P = 0.003$). Variance exceeding 10% occurred more frequently with LDT 0.5 and 1 mL syringes, medication cup dispensing (liquid or tablet) and inappropriate LDT adapter use. Unapproved adapter processes compared to FDA-approved processes held a higher likelihood of unacceptable dosing variance (28% vs 7.4%, $P < 0.001$). FDA-approved use of adapters with prefilled syringes compared to bedside administration may result in higher rates of dosing inaccuracy (18.8% vs 5.6%, $P = 0.06$).

What is new and conclusions: This study raises clinical concerns of dosing inaccuracies with the LDT syringes, particularly with 0.5 and 1 mL sizes. The use of adapters significantly increases the opportunity for inaccurate dosing.

KEYWORDS

adverse event, consumers, drug-related, infants, medicine use, paediatrics, pharmacists, premature neonates, skills training

1 | WHAT IS KNOWN AND OBJECTIVE

Tubing misconnections can lead to patient injury and mortality when compatible devices deliver medications to physiologically incompatible systems, such as when an enteral syringe is connected to an intravenous catheter. In a review of 300 reports, enteral tubing misconnections represented nearly 40% of all cases, with 21 associated fatalities.[1,2] A root cause analysis of these events demonstrated

that interchangeability of luer connectors was likely the primary cause. In response, a Joint Commission sentinel event was released warning healthcare providers about the risk of misconnections.[2]

The International Organization for Standardization (ISO) is an independent, non-governmental organization that provides international standards for medical devices. To reduce the incidence of misconnections, ISO created small-bore connector standards (ISO 80369) for liquids and gases in healthcare applications.[3] ISO 80369-3 was developed for enteral systems, specifying device criteria without limit on manufacturer design application.[4] The Global Enteral Device Supplier Association (GEDSA) was formed in 2013 by manufacturing companies to develop an enteral design adherent to ISO 80369-3 criteria. The female design creates a reverse orientation from the legacy male designs used in most US healthcare systems today. GEDSA supports the female system and recommends international conversion to this design.[5] While no federal regulatory requirements currently exist in the United States to dictate which devices healthcare systems must use, position statements supporting the use of ENFit® as an option for preventing tubing misconnections have been released.[6,7]

Several concerns have emerged as female systems have begun to appear in healthcare settings.[8,9] In addition to operational challenges in the implementation process, potential significant safety risks have been noted. Although intravenous syringes must yield no more than 5% dosing variance, no such standards exist specifically for enteral device performance.[10] Clinically acceptable variability is generally ±10% for low-risk medications, but this may be unacceptable for high-risk medications.[11] The standard female syringe allows for significant dead space in the syringe tip (up to 0.2 mL), yielding unacceptable dosing variance and excessive drug delivery with low volume doses.[12] Concerns amongst healthcare providers regarding dosing accuracy, particularly in paediatric patients, led to the development of the low dose tip (LDT) female syringe (sizes: 0.5, 1, 6 mL) for drug volumes < 5 mL.[13,14] The LDT has a male lumen inside of the standard female tip to reduce the amount of dead space within it. However, the unique female connector on the outer edge of the syringe tip preserves the risk of inadvertent overdose if not completely cleared of drug prior to administration. Although not required by the Federal Drug Administration (FDA), GEDSA recommends use of dispensing adapters to fill LDT syringes to deliver higher dosing accuracy and to reduce potential excess residual drug outside the fluid pathway.[13]

No peer-reviewed literature has explicitly evaluated the low dose tip feature or the use of its associated dispensing and administration adapters. Addition of these items requires stringent adherence to a more complex dispensing and administration process compared to legacy devices (Table 1).[15] Increased complexity can result in increased chance of medication errors, where each new step introduced creates additional opportunity for mistakes.[16] In addition to new instructions for syringe filling, the LDT may require adapters for dispensing and oral administration, representing a source of dosing inaccuracy unless used specifically as instructed every time.[17,18]

Given the lack of peer-reviewed data prospectively evaluating female device performance and its impact on medication administration, this study aims to address clinical concerns of dosing accuracy and the impact of LDT syringes with adapters compared to legacy

TABLE 1 Legacy and ENFit filling and administration processes with adapters

Syringe type	FDA-approved instructions for use	DoseMate	DoseMate DL: bedside fill	Dose mate-DL: Prefilled syringe
Legacy	1. Ensure that the plunger is fully depressed before filling dispenser. 2. Draw medication into dispenser. For accurate measurement, use the edge of the black silicone ring closest to the medication. 3. Slowly depress plunger, directing fluid towards inside cheek to allow for natural swallowing. Forceful squirting to the back of the throat may cause choking.	N/A	N/A	N/A
ENFit	1. Ensure that the plunger is fully depressed before filling dispenser. 2. Draw medication into dispenser. For accurate measurement, use the edge of the black silicone ring closest to the medication. 3. For syringe sizes 6 mL and below, ensure the moat is free of fluids and re-verify doses (repeat as necessary). 4. Before feeding, to minimize potential for clogging, mix any supplements or additives thoroughly to achieve uniform consistency. 5. Slowly depress plunger, directing fluid towards inside cheek to allow for natural swallowing. Forceful squirting to the back of the throat may cause choking.	•Screw adapter completely onto syringe. NOTE: No clarification on bedside fill & prefilled scenarios.	▪Screw adapter completely onto syringe *prior* to drawing up medication from cup.	•Screw adapter completely onto prefilled syringe. NOTE: Approximate priming volume is 0.1 mL. Air flushing may be used to fully expel syringe contents.
		Manufacturer recommendations: Dosing accuracy is maximized when ENFit compatible connectors are used throughout the process of filling, plunger operation and dispensing.		

TABLE 2 Testing conditions with number of tests completed and appropriateness of use by route

Dispense conditions			Administration conditions			
Dosage form	Source	Adapter for drawing up	No adapter		DM-DL	DM
			Legacy (n = 108)	SF + LDT (n = 156)	SF + LDT (n = 156)	SF + LDT (n = 156)
Liquid	Medicine cup	None	42[a]	24[a]	24	24
Liquid	Medicine cup	DM-DL	N/A	24	24[a]	24
Liquid	Medicine cup	DM	N/A	24	24	24[a]
Liquid	Medicine cup	Pharmacy straw	N/A	24[a]	24[a]	24
Liquid	Bulk bottle	None	42[a]	24[a]	24[a]	24
Crushed tablet	Medicine cup	None	24[a]	12[a]	12	12
Crushed tablet	Medicine cup	DM-DL	N/A	12	12[a]	12
Crushed tablet	Medicine cup	DM	N/A	12	12	12[a]

DM, DoseMate®; DM-DL, DoseMate DL®; LDT, low dose tip; SF, standard female.
[a]Appropriate per FDA-approved instructions for use and/or manufacturer recommendations.

devices. The primary objective of this study was to evaluate the frequency of dosing variance exceeding 10% of the intended dose between legacy and the female LDT syringes. Secondary objectives include the evaluation of overall dosing performance of female and legacy designs, and the impact of drug volume, dispense method and use of adapters on dosing accuracy.

2 | METHODS

An in vitro study was conducted at UF Health Shands Hospital in conjunction with the University of Florida College of Pharmacy. Three types of enteral medication syringes (Baxter® legacy, NeoMed® legacy, and NeoMed® ENFit®) were evaluated. Four syringe sizes commonly used for oral medication administration were selected (Baxter® legacy: 0.5, 1, 5, 10 mL; NeoMed® legacy: 0.5, 1, 6 mL; NeoMed® ENFit®: 0.5, 1, 6, 12 mL). Two intended volumes were evaluated per syringe based on NeoMed® syringe sizes: a low intended volume (LV: 20% of syringe capacity) and a high intended volume (HV: 80% of syringe capacity). The 12-mL ENFit® device was used as a control for female syringe performance. A single investigator performed all testing.

For syringe filling, the FDA-approved instructions for use were followed (Table 1).[17] For the LDT, the moat was cleared completely by tapping or flicking the syringe tip before each measurement was obtained. The moat was defined as the area surrounding the interior lumen that can serve as reservoir of drug if not cleared completely prior to administration. Potential conditions for use of the ENFit® syringes and adapters were tested in several predetermined combinations (Table 2). ENFit® connectors included the DoseMate® (DM: nipple-shaped adapter) and DoseMate DL® (DM-DL: straw adapter), pharmacy straw and bulk bottle pharmacy cap.

Federal Drug Administration-approved instructions for use and manufacturer recommendations were followed for each adapter piece.[18] DoseMate DL® instructions delineate separate procedures for prefilled syringes (attached prior to administration) and bedside use (attached and used throughout filling and administration). Syringes filled from bulk bottles with the pharmacy adapter cap and pharmacy straw were considered "prefilled" syringe conditions since these methods are most utilized by inpatient pharmacy for patient-specific doses. Medicine cup dispensing was considered a "bedside" condition, as this is most likely to occur by the nurse or caregiver directly prior to administration. To be qualified as "appropriate" device use, only conditions meeting the FDA-approved instructions for use were evaluated. For the DoseMate®, general manufacturer recommendations were followed because the instructions for use did not provide clear details for how it must be used. Tests deemed "inappropriate" were any conditions/combinations that were not explicitly outlined by the manufacturer or instructions for use. An example of this would include using a pharmacy straw for dispensing and attaching a DoseMate® adapter for administration. Dead space for each syringe was considered the area within the tip where drug may remain after administration. Priming volume was considered the volume needed to fill the oral adapter pieces.

Two commonly used oral medications and formulations in the paediatric population were selected for study. Brompheniramine maleate/dextromethorphan HBr/phenylephrine HCl oral liquid (Children's Dimetapp Cold & Cough; Pfizer, Inc, Sanford, NC, USA) was chosen to represent a common outpatient medication, and aspirin 81 mg chewable tablets (chewable aspirin; Equate) was chosen for its use in infants and children with cardiac or vascular diseases. A Mettler Toledo® ME303E electronic scale was used for measuring all tests (precision/accuracy = 0.001 g).[19] A preweighed graduated cylinder and Eppendorf pipettor were utilized with the scale to determine density and specific gravity of the brompheniramine maleate/dextromethorphan HBr/phenylephrine HCl oral liquid and aspirin tablet. Aspirin was crushed into a uniform powder and weighed before crushing and was mixed with 1 mL of water. Water samples were used to verify the accuracy of the specific gravity calculations. This process was repeated three times. The testing for crushed tablets

was only performed in the low dose tip (0.5 and 1 mL) and legacy syringes. These syringes sizes would typically be available on a nursing unit for the nurse to crush and draw up medications. Other dispensing methods were tested in all four syringe sizes (0.5, 1, 6 and 12 mL).

Dosing accuracy of legacy syringes was assessed by drawing up medication from an oral bulk bottle or medication cup and administering without adapters. Female design performance was assessed with various adapter conditions (Table 2). Before all tests, a dry weight was obtained for each size syringe, ENFit® DoseMate® and DoseMate DL® adapters, and the pharmacy straw. After filling the syringe to the intended volume, the syringe was re-weighed. The contents of the syringe were expelled into a tared medication boat to determine the administration dose in grams. Specific gravity was used to calculate the volume administered in millilitres (mL). Each test condition was repeated three times to ensure consistency and reproducibility. Dosing variance was calculated for each test by dividing the difference between the actual volume and intended volume by the intended volume. Dosing variance exceeding 10% of the intended dose was considered unacceptable. Statistical analysis was completed using JMP Pro vs 13.0.0 and compared for accuracy. Chi-square/Fisher's exact test, *t* test, ANOVA and descriptive statistics were used as appropriate.

3 | RESULTS AND DISCUSSION

3.1 | Overall performance

In total, 576 tests were evaluated (legacy = 108, female LDT = 378, standard female = 90). The breakdown of each test performed is reported in Table 2. Twenty-four total ENFit® syringe conditions were evaluated, with only 10 of these considered strictly compliant with FDA-approved instructions for use/manufacturer recommendations. The LDT had a higher rate of dosing variance > 10% compared to standard female and legacy syringes (Table 3). Compared to legacy, all female syringes resulted in a significantly higher frequency of tests reaching unacceptable dosing variance (Table 3). Dosing variance ranged from −27% to 15.5% for legacy products, −99% to 14.3% for LDT syringes and −7.7% to 11.4% for the standard female (Figure 1).

3.1.1 | Syringe size

Dosing variance was further stratified by syringe size (Table 3). The combined test of all LDT syringes (0.5, 1, 6 mL) compared to legacy demonstrated significantly higher dosing inaccuracy with the LDT. The incidence of dosing variance exceeding 10%, and absolute variance were significantly greater for 0.5 and 1 mL LDT syringes compared to legacy. There was no difference found between the 6 and 12 mL female and legacy syringes.

3.1.2 | Dosing volume

The impact of dosing volume on syringe performance is described in Table 4. The incidence of dosing variance > 10% was greater in the 0.5 mL/low volume LDT tests compared to legacy syringes. There were no statistical differences found between high volume tests in any syringe size at 10% variance. When evaluating dosing variance > 5%, there were significantly more LDT syringe tests exceeding the target dose with the 0.5 mL/low volume and 1 mL/high

TABLE 3 Overall dosing variance and frequency of tests exceeding 10% DV

	Legacy	Female	*P*-value
All syringes[a]	N = 108	N = 468	
DV > 10%, n (%)	8 (7.4)	99 (21.2)	0.003
Absolute DV, mean %	3.9	8.1	0.0009
LDT (0.5, 1, 6 mL)	N = 96	N = 378	
DV > 10%, n (%)	8 (8.3)	98 (25.9)	<0.0001
Absolute DV, mean %	4.2	9.6	<0.0001
0.5 mL Syringes	N = 36	N = 144	
DV > 10%, n (%)	5 (13.9)	57 (39.6)	0.002
Absolute DV, mean %	5.4	15.4	<0.0001
1 mL syringes	N = 36	N = 144	
DV > 10%, n (%)	2 (5.6)	38 (26.4)	0.003
Absolute DV, mean %	3.6	8	0.01
6 mL syringes	N = 24	N = 90	
DV > 10%, n (%)	1 (4.2)	3 (3.3)	0.84
Absolute DV, mean %	3.4	2.7	0.29
12 mL syringes[a]	N = 12	N = 90	
DV > 10%, n (%)	0 (0)	1 (1.1)	0.62
Absolute DV, mean %	0.9	1.2	0.04

DV, dose variance, LDT, low dose tip
[a]Includes standard female syringes.

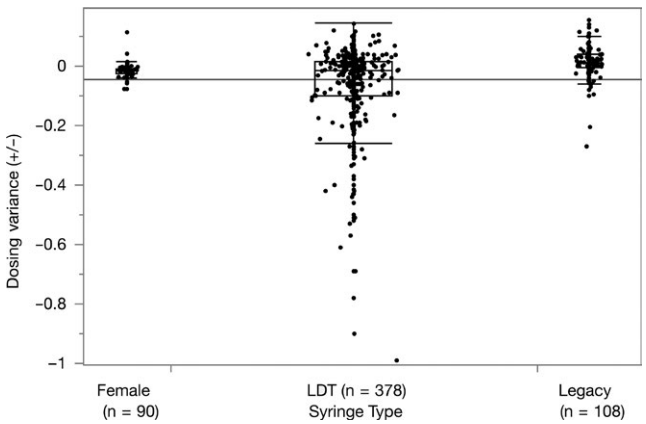

FIGURE 1 Dosing variance by syringe type. It displays the dosing variance by syringe type for all conditions tested. LDT, low dose tip

TABLE 4 Dose variance based on dosing volume

Syringe size	Test volume	Legacy N = 18	LDT N = 72	*P*-value
0.5 mL	Low volume			
	Doses within 10%, n (%)	15 (83.3)	30 (41.7)	0.001
	Doses within 5%, n (%)	9 (50)	15 (20.8)	0.02
	High volume			
	Doses within 10%, n (%)	16 (88.9)	57 (79.2)	0.32
	Doses within 5%, n (%)	14 (77.8)	43 (59.7)	0.14
1 mL	Low volume			
	Doses within 10%, n (%)	16 (88.9)	42 (58.3)	0.05
	Doses within 5%, n (%)	12 (66.7)	30 (42)	0.05
	High volume			
	Doses within 10%, n (%)	18(100)	64 (88.9)	0.05
	Doses within 5%, n (%)	18 (100)	(46 (63.9)	0.003

LDT, low dose tip

volume. To quantify the mean absolute dosing variance exceeding 10%, the 0.5 mL LDT yielded 38.3% (low volume tests) and 16.7% variance (high volume tests). The mean absolute dosing variance for tests exceeding 10% with the 1 mL LDT was 19.5% (low volume tests) and 22.2% (high volume tests).

3.1.3 | Dispense method

Comparing the frequency of dosing variance exceeding 10% by dispense method, the bulk bottle was associated with a significantly lower rate compared to medication cups or crushed tablets, 7.9% vs 16.4% vs 33.3% ($P < 0.001$), respectively. Female syringes were more likely to result in dosing variance > 10% with medicine cups (18.4% vs 2.4%, $P = 0.002$) and crushed tablet dispensing (38.9% vs 8.3%, $P = 0.002$). There were no statistically significant differences seen between syringe types for bulk bottle dispensing.

3.1.4 | Adapters

Lastly, when evaluating the impact on dosing variance > 10% with adapters (n = 204) used in accordance with FDA-approved instructions for use compared to legacy (n = 108), there was no difference (12.3% vs 7.4%, $P = 0.17$). Inappropriate adapter processes (n = 264) compared to legacy (n = 108) held a higher likelihood of unacceptable dosing variance (28% vs 7.4%, $P < 0.001$). Likewise, when comparing unapproved (n = 264) to approved adapter processes (n = 204), the difference was also significant (28% vs 12.3%, $P < 0.001$). Using approved DoseMate DL® instructions for use, "prefilled syringe" (n = 48) conditions were associated with higher rates of dosing variance > 10% than "bedside administration" (n = 36) conditions (18.8% vs 5.6%, $P = 0.06$).

Preventing tubing misconnections while preserving dosing accuracy are key targets for novel enteral device systems. One of the most challenging aspects of evaluating data for enteral syringes is that no standard exists for acceptable device performance/dosing accuracy. Although male intravenous syringes are designed to deliver no more than ±5% variance when the syringes are filled at least 50%, no such standard currently exists for enteral/oral syringes.[4,10] Most clinicians accept up to 10% variability in other areas of clinical practice, such as with dose rounding in computerized physician order entry systems. For medications with a narrow therapeutic index (NTI) or with high risk of dose-dependent toxicity, published acceptable variance is only up to 5 per cent.[10]

When testing the female LDT syringes across potential dispensing and administration conditions, the overall rate of dosing variance > 10% in our study was nearly three times higher than with legacy. The 0.5-mL LDT syringe was particularly vulnerable to high rates of unacceptable dosing variance when used for low intended dosing volumes. For tests falling outside acceptable dosing variance, the mean variance ranged from nearly 20% to 40% depending on syringe size and volume tested. This is especially concerning for dosing accuracy in high-risk patients, such as neonates and paediatrics, who often receive small volumes of highly concentrated oral liquid medications. Potentially, problematic medications include concentrated morphine, digoxin, tacrolimus and electrolyte supplementations. For example, in a 1 kg neonate whose intended digoxin (50 mcg/mL oral liquid) dose is 5 mcg (0.1 mL), 20% dosing variance could mean the patient receives 4-6 mcg of medication. Based on a dose of 5 mcg/kg, the difference in dose is ±1 mcg/kg/dose. Neonates in the United States are exposed to an average of four medications per neonatal intensive care unit admission, with premature neonates receiving an average of seventeen.[20,21] Although the authors do not state what

TABLE 5 Common high-risk paediatric/neonatal medications[a]

Medication	Concentration	Neonatal dose (volume)	20% DV (volume)	Paediatric dose (volume)	20% DV (volume)
Tacrolimus	0.5 mg/mL	--	--	1 mg (2 mL)	0.2 mg (0.4 mL)
Cyclosporine	100 mg/mL	--	--	20 mg (0.2 mL)	4 mg (0.04 mL)
Phenytoin	125 mg/5 mL	6 mg (0.24 mL)	1.2 mg (0.05 mL)	20 mg (0.8 mL)	4 mg (0.16 mL)
Phenobarbital	20 mg/5 mL	3 mg (0.75 mL)	0.6 mg (0.15 mL)	20 mg (5 mL)	4 mg (1 mL)
Clonidine	10 mcg/mL	1 mcg (0.1 mL)	0.2 mL (0.02 mL)	33 mcg (3.3 mL)	6.6 mcg (0.66 mL)
Clonazepam	0.1 mg/mL	0.1 mg (1 mL)	0.02 mg (0.2 mL)	1 mg (10 mL)	0.2 mg (2 mL)
Morphine	2 mg/mL	0.1 mg (0.5 mL)	0.02 mg (0.01 mL)	1 mg (0.5 mL)	0.2 mg (0.1 mL)
Methadone	2 mg/mL	0.1 mg (0.05 mL)	0.02 mg (0.01 mL)	1 mg (0.5 mL)	0.2 mg (0.1 mL)
Gabapentin	50 mg/mL	5 mg (0.1 mL)	1 mg (0.02 mL)	50 mg (1 mL)	10 mg (0.2 mL)
Digoxin	50 mcg/mL	5 mcg (0.1 mL)	1 mcg (0.02 mL)	50 mcg (1 mL)	10 mcg (0.2 mL)
Enalapril	1 mg/mL	100 mcg (0.1 mL)	20 mcg (0.02 mL)	1 mg (1 mL)	0.2 mg (0.2 mL)
Zidovudine	10 mg/mL	3 mg (0.3 mL)	0.6 mg (0.06 mL)	60 mg (6 mL)	12 mg (1.2 mL)
Lamivudine	10 mg/mL	2 mg (0.2 mL)	0.4 mg (0.04 mL)	50 mg (5 mL)	10 mg (1 mL)

[a]Medication amounts using 20% dosing variance for 1 kg neonate and 10 kg paediatric patients

percentage of these medications were given orally, nearly half of the top medications listed are only available orally or have an oral dosage formulation option. As the patients most likely to receive medications via LDT syringes due to small dosing volumes, the opportunities for exposure, risks and impacts of inaccurate dosing are highest in the smallest of patients. Although neonates are exquisitely susceptible to negative outcomes with medication dosing errors, this holds true for patients across all facets of health care requiring liquid medications due to age, mental status or physical limitations.[22] Examples of commonly used medications in neonates and paediatrics that could result in detrimental outcomes if inaccurate doses are delivered are summarized in Table 5.[23] It is important to note that the seemingly small variations in volumes delivered demonstrated in this study can carry significant clinical implications in paediatrics and neonates receiving high-risk medications.

In addition to the lack of consistency in oral/enteral device standards, sparse data are available regarding clinical evaluation of the female syringe system. A non-peer-reviewed poster by Deken et al[24] studied 1-mL syringes (standard female, female with LDT, reverse luer lock and legacy) to determine dosing variance when syringes were filled directly from a medication cup or with a straw. It is unclear if the straw used was in a medicine cup or if it was a pharmacy straw used with a bulk bottle. The authors do not state what volumes they measured, or if it was consistent across each of the test conditions. The data provided visually appears to show a difference in the performance of the three different legacy brands tested, but this is impossible to determine given the data for all three syringes are pooled in the results. Additionally, the authors evaluated the impact of positioning of the feeding tube, but it is unclear how the final assessment of delivered dose was measured. They conclude that the female LDT performance was substantially equivalent to existing male oral syringes, but without providing key methodological information such as the sample size needed, statistical evaluation used and choice of quantitative boundaries to establish statistically significant equivalence, and this conclusion is difficult to validate.[25] Testing across a combination of conditions applicable to enteral use of the standard female and LDT provides some valuable information that is otherwise lacking in the literature. This study did not evaluate the impact of administration adapters, which is important for consideration in patients who may receive drugs by mouth with female syringes.

Single-use adapters are available for use with the LDT syringes to minimize patient discomfort during oral delivery secondary to a phalange on the syringe tip.[12] LDT syringe adapters for oral use are not explicitly required per the syringe instructions for use, but many clinicians feel they are vital for infants to minimize risk of oral tissue damage. The manufacturer states that the DoseMate® is a critical component necessary for standardizing with ENFit devices that comply with GEDSA's position statement on dosing accuracy.[18] This apparent contradiction in requirement for use may create an operational challenge and variation in clinical practice. The manufacturer recommendations for oral adapters state that dosing accuracy is maximized when the same connectors are used throughout the process of filling, plunger operation and dispensing, and our findings confirm this. Using a different adapter for dispensing than administering or using adapters for only dispensing or administering can result in significant dosing inaccuracy.

The DoseMate DL® arguably has the largest impact on inpatient medication dispensing and administration. The instructions for use explicitly state that when used for bedside administration, the DoseMate DL® should be added to the syringe before drawing up the medication and maintained through the entire dispensing and administration process. For prefilled syringes, such as those dispensed in ready-to-use formats from inpatient pharmacy, the instructions state that the adapter should be attached prior to administration only. Of note, the DoseMate DL® has 0.1 mL priming

volume, which may require air flushing to fully expel the syringe contents when used on a prefilled syringe. The instructions do not require flushing to clear the priming volume. Failure to do so could result incomplete delivery of medication and under-dosage. Our study results support this premise, suggesting that dosing accuracy may be compromised when the DoseMate DL® is attached prior to administration. The contradictory statements between the FDA-approved instructions for use and manufacturer's recommendations, particularly as it pertains to prefilled syringes, should be resolved for clarity in clinical use.

Adapter use carries new expectations, so nurses and caregivers will need extensive training to understand how to appropriately use these features and their potential impact on dosing accuracy. This study tested 24 possible combinations, but less than half of these would strictly meet the FDA-approved instructions for use. Given the large number of potential unapproved combinations that could be utilized, the threat of compromised dosing accuracy is high. Failure to use dispensing adapters altogether may increase risk to patients from exposure to excessive medication if the syringe tip is not completely cleared of medication.[13] It is important to consider the education levels, healthcare literacy and access to resources of patients and caregivers for use of these devices in the outpatient setting. Table 1 outlines the increased complexity of use between legacy and both types of female syringes. LDT syringes with adapters essentially double the number of steps required for proper administration, creating opportunity for error with increased time and steps for completion.[16] Increased device complexity cannot be ignored as a potential source of significant medication error in medically complex paediatric patients who may be unable to verbalize experience of adverse effects.

A.S.P.E.N. has published recommendations for use of female syringes in both inpatient and home care settings, giving instructions for use filling with a straw, bottle adapter and medication cup.[26] These instructions focus on the enteral route and lack information for oral use, including how to utilize adapters for administration. Since some patients may utilize both enteral and oral routes, it is essential that caregivers understand the dosing accuracy risks with adapters. Furthermore, different administration routes may require different dispensing processes and adapter applications. This needs to be clearly outlined to caregivers and patients so that a safe, consistent process is developed to minimize risk of inaccurate dosing.

For all syringe types, dosing accuracy is compromised when administering doses from medication cups compared to bulk bottles with compatible pharmacy adapter caps. Female syringes performed poorly against legacy syringes for dispensing of liquids and crushed tablets from medication cups. When testing a standard crushed chewable aspirin tablet dispersed in water, the small bore diameter of the adapters clogged easily. This may lead to under-dosing if not all of the intended dose is delivered or over-dosing if the caregiver attempts to give extra medication to make up for the amount lost.

This is the first study that we are aware of that highlights the dosing inaccuracies that can occur with the use of ENFit® adapter pieces. One methodologic limitation is the lack of availability of consistent syringe sizes between manufacturers, leading to slightly different dose volume percentages based on total syringe capacity. This study only considered bulk bottles with compatible syringes and medication cups with pharmacy straws as ready-to-use syringes, but other pharmacy dispensing methods may be utilized at different facilities based on drug availability and institution-specific factors. Because only a small number of proprietary brands of syringes were studied, and no device standards exist, different brands may perform with different rates of dose accuracy. Development of standardized enteral device performance criteria are needed to objectively evaluate currently available and future product line designs.

4 | WHAT IS NEW AND CONCLUSIONS

This study raises clinical concerns with the dosing accuracy of female low dose tip syringes and associated adapters. While is it beyond the scope of this study to fully elucidate the clinical impact of inaccurate small volume doses, clinicians whose patient populations include those receiving low volume oral medications should be aware of the potential impact on drug delivery. Contradictory statements between the FDA-approved instructions for use of the syringes/adapters and the manufacturer's general recommendations may cause confusion and inconsistency with how this information is applied in clinical practice. Extensive patient and caregiver education taking into account financial, educational and practical considerations will be a critical component of establishing safe practices in the outpatient setting.

ACKNOWLEDGEMENTS

Dr. Cary Mobley for his contributions to the experimental design.

REFERENCES

1. Staebler S. Enteral feeding misconnections in the NICU: a continuing patient safety threat. *Adv Neonatal Care*. 2013;13(6):447-453.
2. The Joint Commission. Managing risk during transition to new ISO tubing connector standards. *Sentinel Event Alert*. 2014;23:1-6. https://www.jointcommission.org/assets/1/6/SEA_53_Connectors_8_19_14_final.pdf. Accessed April 23, 2018.
3. ISO 80369-1: Small-bore connectors for liquids and gases in healthcare applications. International Organization for Standardization Website. https://www.iso.org/obp/ui/#iso:std:45976:en. Published December 2010. Accessed April 23, 2018.
4. ISO 80369-3: Small-bore connectors for liquids and gases in healthcare applications – Part 3: Connectors for enteral applications. International Organization for Standardization Website. https://www.iso.org/obp/ui/#iso:std:50731:en. Published July 2017. Accessed April 29, 2018.
5. Reducing the risk of medical device tubing misconnections. Stay Connected Website. http://stayconnected.org/wp-content/uploads/2016/09/ESPEN-Presentation.pdf. Accessed April 23, 2018.
6. Institute for Safe Medication Practices. Targeted Medication Safety Best Practices for Hospitals Website. https://www.ismp.org/guidelines/best-practices-hospitals. Accessed September 12, 2018.

7. U.S. Food and Drug Administration MedWatch-The FDA Safety Information and Adverse Event Reporting Program Website. The FDA Encourages Use of Enteral Device Connectors that Reduce Risk of Misconnection and Patient Injury. https://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM619782.pdf?utm_campaign=FDA%20MedWatch%20-%20The%20FDA%20Encourages%20the%20Use%20of%20Enteral%20Device%20Connectors&utm_medium=email&utm_source=Eloqua. Accessed September 12, 2018.
8. Institute for Safe Medication Practices. ENFit enteral devices are on their way…Important safety considerations for hospitals. ISMP Medication Safety Alert Website. http://www.ismp.org/newsletters/acutecare/showarticle.aspx?xml:id=105. Published April 9, 2015. Accessed April 23, 2018.
9. Bledsoe S, Oschman A, Hampson K, Hoebing W, Pabst D. Transition to ENFit enteral devices: special challenges for pediatric institutions. *Am J Health Syst Pharm*. 2016;73(21):1781-1783.
10. ISO 7886-1:2017. Sterile hypodermic syringes for single use—Part 1: Syringes for manual use. International Organization for Standardization. Website. https://www.iso.org/standard/64790.html. Published May 2017. Accessed April 29, 2018.
11. Johnson KB, Lee CK, Spooner SA, Davison CL, Helmke JS, Weinberg ST. Automated dose-rounding recommendations for pediatric patients. *Pediatrics*. 2011;128(2):e422-e428.
12. Institute of Safe Medication Practices. Low dose enteral syringe tip gets FDA Clearance. ISMP Medication Safety Alert Website. https://www.ismp.org/resources/low-dose-enteral-syringe-tip-gets-fda-clearance. Published August 11, 2016. Accessed April 23, 2018.
13. GEDSA ENFit® Low dose tip syringe review. Website. http://stayconnected.org/wp-content/uploads/2016/04/GEDSA-Low-Dose-Syringe-End-User-LDT-Preso-FINAL.pdf. Accessed May 14, 2018.
14. ENFit advocacy meeting. Stay Connected. http://stayconnected.org/wp-content/uploads/2017/08/ENFit-Advocacy-Meeting-uploadv2.pdf. Accessed March 20, 2018.
15. Procedure for inpatient settings: preparing and administering medications using ENFit. Stay Connected Website. http://stayconnected.org/wp-content/uploads/2016/11/11-07-16_InfoGraphic_-Inpatients_-FINAL.pdf. Accessed March 20, 2018.
16. McDowell SE, Ferner HS, Ferner RE. The pathophysiology of medication errors: how and where they arise. *Br J Clin Pharmacol*. 2009;67(6):605-613.
17. ENFit compliant NeoConnect pharmacy syringes. Website. https://www.neomedinc.com/product/neoconnect-pharmacy-syringes/. Accessed April 28, 2018.
18. ENFit Compatible NeoConnect DoseMate and DoseMateDL. NeoMed Website. https://www.neomedinc.com/product/neoconnect-dosemate-oral-administration-tip/. Accessed May 11, 2018.
19. Mettler Toledo. https://www.mt.com/in/en/home/products/Laboratory_Weighing_Solutions/Precision_Balances/Standard/ME_Precision_Balances/me303e-a04.html. Accessed May 11, 2018.
20. Krzyzaniak N, Bajorek B. Medication safety in neonatal care: a review of medication errors among neonates. *Ther Adv Drug Saf*. 2016;7(3):102-119.
21. Hsieh E, Hornik CP, Clark RH, et al. Medication use in the neonatal intensive care unit. *Am J Perinatol*. 2014;31(9):811-822.
22. Kaushal R, Bates D, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA*. 2001;285:2114-2120.
23. Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2009;10(1):85-90.
24. Deken A, Davis B, Giles A, Koepler C, McMichael D, Phillips P. Dose accuracy-performance testing of enteral, oral, ENFit, and ENFit LDT syringes. http://stayconnected.org/wp-content/uploads/2016/10/GEDSA-ENFit-LDT-Research-Poster.pdf. Accessed May 8, 2018.
25. Greene C, Morland L, Durkalski V, Frueh BC. Noninferiority and equivalence designs: issues and implications for mental health research. *J Trauma Stress*. 2008;21(5):433-439.
26. A.S.P.E.N. Enfit ® syringe medication delivery procedures. Website. http://www.nutritioncare.org/News/General_News/ENFit®_Syringe_Medication_Delivery_Procedures/. Accessed September 13, 2018.

How to cite this article: O'Mara K, Gattoline SJ, Campbell CT. Female low dose tip syringes-increased complexity of use may compromise dosing accuracy in paediatric patients. *J Clin Pharm Ther*. 2019;00:1–8. https://doi.org/10.1111/jcpt.12810