JPPT | Single-Center Simulation Study

Physical Compatibility of Y-site Pediatric Drug Administration: A Call for Question of US Pharmacopeia Standards?

Emma L. Ross, PharmD; Kirsten Petty, PharmD; Allison Salinas, PharmD; Jarrett Bremmer, PharmD; Cheng Her, PhD; and John F. Carpenter, PhD

OBJECTIVE To evaluate the physical intravenous Y-site compatibility of 29 combinations of medications at commonly used pediatric concentrations using both existing and novel techniques.

METHODS Medication combinations included were selected by a varied group of pediatric inpatient pharmacists, and then assessed by 3 independent reviewers for existing literature. For each combination, 2 different medications were mixed together in a 1:1 ratio and incubated at room temperature for 4 hours to simulate Y-site administration. Each sample was then analyzed using the US Pharmacopeia (USP) <788> recommended analytical technique of light obscuration (LO) in addition to novel flow imaging (FI) microscopy and backgrounded membrane imaging (BMI). Physical compatibility was determined using USP chapter <788> large volume particle count limits for all techniques.

RESULTS A total of 29 different medication combinations were studied. Five combinations met criteria for compatibility by all 3 techniques. The remaining 24 combinations reached the threshold to be considered incompatible by at least 1 of the 3 techniques. Light obscuration, BMI, and FI identified 14%, 59%, and 76% of combinations as incompatible, respectively. All samples deemed incompatible by LO were also incompatible by at least 1 of the other 2 techniques. Flow imaging and BMI results agreed in 69% of samples tested.

CONCLUSIONS Most combinations tested were found to be incompatible by at least 1 of the 3 instruments used. Light obscuration appears to have reduced accuracy for identifying particulate resulting in physical medication incompatibility when compared with the novel techniques of FI and BMI.

ABBREVIATIONS BMI, backgrounded membrane imaging; D5W, 5% dextrose in water; FI, flow imaging; IV, intravenous; LO, light obscuration; NS, normal saline; USP, US Pharmacopeia

KEYWORDS drug stability; intravenous administration; intravenous infusion; particulate matter; pediatrics

J Pediatr Pharmacol Ther 2023;28(1):84–93

DOI: 10.5863/1551-6776-28.1.84

Introduction

Significant challenges exist related to safe intravenous (IV) medication coadministration in the pediatric patient. To maintain homeostasis, critically ill pediatric patients often require many IV medications. An infant in the neonatal intensive care unit may receive 8.5 (±8.3 SD; range 1–62) IV medications during a single admission.[1] Children in the pediatric intensive care unit have been reported to receive as many as 49 IV medications.[2] Due to medication-specific challenges in pediatric patients, medications are often prepared and administered at different concentrations than are typically used for adults. These concentrations often vary when compared with those used in adult patients, particularly due to higher nutrition requirements necessitating a large percent of an infant's total fluid intake to be nutritionally effective. Although some data are available for physical compatibility of IV medications at concentrations commonly used in adults, this information is often not available for the medications and/or concentrations commonly administered to children. Medication physical compatibility can vary based on the concentration of the drugs, as well as the duration of the infusion.

Incompatible IV medications may form particles that may be visible, but the particles are often not visible to the unaided eye. A recent evaluation of particulate matter infused in a neonatal intensive care unit demonstrated that infants may receive up to 85,000 subvisible particles from IV medications per day, when receiving multidrug IV therapies.[3] The infusion of subvisible particles is implicated in microcirculatory impairment, leading to severe complications including pulmonary dysfunction, cardiovascular arrest and multiorgan failure.[4–6] Studies of IV particle administration in animal models have demonstrated acute kidney injury, decreased glo-

merular filtration rates, and myocardial damage leading to reduced coronary blood flow.[7,8] Furthermore, the suppression of macrophage and endothelial cell cytokine secretion *in vitro* suggests that infusions of high particle loads may have negative immune-modulating effects in pediatric patients.[9] Particulate contamination of IV fluids may have life-threatening consequences in the critically ill infant, and coadministering medications that have not been evaluated for physical compatibility increases the risk of unknowingly administering particles to patients.

Methodology for evaluating particulate matter in injectable products is defined in US Pharmacopeia (USP) chapter <788>.[10] Light obscuration (LO) and microscopic particle count tests are the 2 specific methods within the pharmacopeia for quantifying subvisible particles. However, use of new analytic techniques such as flow imaging (FI) and backgrounded membrane imaging (BMI) allow for improved identification of particle morphology. They also allow for a more accurate characterization of particles in solution and may provide greater insight into the particulate being infused.[11–13]

Pediatric patients often receive multiple IV medications via Y-site connection, which infuse together through a single lumen. This is because it is common to face significant challenges related to obtaining and maintaining reliable vascular access in pediatric patients.[14] Additional vascular line placement presents problems due to limited viable access points and added risk with each line. These risks include infection, hypervolemia, clots, perfusion dysregulation, and extravasation.[15–21] Additionally, obtaining additional vascular access often takes a significant amount of time and may cause a significant delay in critical medication administration.

Due to the relatively slow infusion rates used in pediatric patients, the IV medications can be exposed to each other for long periods of time before entering the bloodstream. Even if an in-line filter is used, there can be significant mixing of the medications downstream of the filter before entering the bloodstream. If there were physical incompatibilities between the medications, there could be sufficient time for particle formation.

In the clinical setting, health care providers are often faced with a difficult decision: the risk of coadministering life-sustaining medications without strong physical compatibility data, or the risks and delays associated with additional vascular access. The purpose of the current study was to determine the physical simulated Y-site compatibilities of specific combinations of commonly used IV medications at standard pediatric concentrations using both existing and novel methods.

Methods

Determination of Combinations to Test. To create a list of medication combinations based on institutional standard concentrations, we surveyed a group of inpatient pediatric clinical pharmacists. The pharmacists were practicing in a variety of subspecialty areas in a freestanding pediatric hospital. The list was then reviewed independently by 3 pediatric clinical pharmacists to evaluate the applicability of any existing data using standard search terminology in PubMed and Trissel's 2 Clinical Pharmaceutics database.[22] The criteria for inclusion of each recommended combination in this evaluation were either a lack of existing compatibility data for the combination or the existing data were for a lower concentration of 1 or both medications compared with what is clinically used in practice at the study institution.

Preparation of Samples. All preparation of samples took place in a USP <797> compliant sterile compounding area in a laminar flow hood by 2 pharmacists with sterile IV medication preparation competency. For each combination, 3 different sample syringes were prepared, 1 on each day of analysis. Further dilutions from manufacturer available concentrations, if required, were compounded using standard compounding instructions specific to this institution with the manufacturer recommended diluent. Medications tested are listed in Table 1. Medication concentrations, diluents (if required) and the drug-drug combinations tested are listed in Tables 2 and 3. All samples were prepared in sterile 10 mL Becton Dickinson (BD) syringes in a 1:1 volume ratio of each medication with another commonly used medication using a fluid dispensing connector (B Braun) or 18-gauge needle. To simulate Y-site infusion compatibility, these syringes were then incubated at room temperature (20°C–22°C) for 4 hours. The pH of the samples was tested immediately after mixing and again at the 4-hour time point using MilliporeSigma MQuant pH test strips.

Analytical Methods for Particles. Visual inspection was the first method performed at the 4-hour time points. Each sample (n = 3 for each combination) was lightly swirled 4 times and then divided into 3 aliquots, 1 for each instrumental method. Each aliquot was gently swirled 4 more times prior to each instrumental method being performed to promote uniform distribution of any possible particulates. The number of measurements completed for each instrumental method varied and was selected to achieve a similar total volume of sample analyzed for each instrument.

Visual Inspection. Each of the 3 samples for each combinations was visually inspected immediately after mixing and at 4 hours using both a white and black background by 2 different investigators independently. The investigators performing the visual analysis were both licensed pharmacists with sterile IV medication preparation competency. Visual detection of the formation of particles, crystals, or cloudiness constituted a positive finding of physical incompatibility. Color change was visually assessed at both timepoints. Gas formation was evaluated as quantity and size (diameter measured in millimeters) of bubbles present upon mixing and at the 4-hour time point and quantification of any gas accumulation within the syringe at both timepoints.

Table 1. Medications Evaluated, Lot Numbers, and Manufacturers

Medication or Diluent	Lot Number	Manufacturer
Alprostadil	C40351	Pfizer
Ampicillin	9A02AS, 0C02AS	Athenex Pharmaceuticals
Ampicillin/sulbactam	AF1520004-a	AuroMedics Pharma
Bumetanide	070075, 030055, 30023, 70103; 18295DD	Westward; Hospira
Calcium chloride	CE039G0	International Medical Systems Limited
Cefepime	0C0175A42	Apotex
Ceftriaxone	LD146579, LD146661	Baxter
Cisatracurium	WT005; 08430DD	Sandoz; AbbVie
D5W NS 20 mEq KCl	Y312371	Baxter
Dexmedetomidine	NC133241, NC113241; NC128414	Baxter; Novaplus
Dihydroergotamine	OC263A	Perrigo
Epinephrine	51081e9	International Medical Systems Limited
Heparin	6020450, 6017918	Fresenius Kabi
Hydromorphone	070953F	Teva
Ketamine	171217A	Mylan
Lacosamide	910206	UCB, Inc
Lactated Ringer's	y336987	Baxter
Milrinone	05313KL	Hospira
Ondansetron	M2006276	Accord
Rocuronium	KJ5443, KD5770	Sandoz
Sildenafil	CSD190003	AuroMedics Pharma
Vancomycin	NC1232770, NC133791	Baxter
Vasopressin	345513	PAR Pharmaceuticals
Dextrose 5%	4339506, Y338554	Baxter
Normal saline	Y340014, Y342087, V20A07A, Y339537	Baxter
Dextrose 50%	10-200-DK	Hospira
Potassium chloride	6022375	Fresenius Kabi
Sterile water for injection	4341561	Baxter

FI Microscopy. We performed microparticle analysis in our research lab using FI via FlowCam VS (Yokogawa Fluid-Imaging Technologies, Inc) instrument for 3 samples of each combination. The sample volume per run was 250 µL. Samples were run as-is and were not diluted, centrifuged, or filtered. The lower particle size for analysis was 1 µ (defined as the lower limit of interest for this evaluation). A standard water wash protocol was used to clean the instrument after each measurement, and the number of microparticles measured in "particle-free" water before each subsequent run was less than 10 particles/mL. Any silicone oil droplet contaminates from the syringe were removed from final particle counts with a filter criterion of circularity ≥0.8 and aspect ratio of ≥0.8. For each of the 3 samples tested, the average particle count was calculated from the values from 9 separate measurements for a total analyzed volume of 2.25 mL of each sample.

Light Obscuration. Microparticle analysis was performed using LO with the HIAC 9703+ (Beckman-Coulter) instrument for 3 samples of each combination. For each analysis, a 1-mL loading volume was used,

Table 2. USP <788> Drug-Drug Combination Cumulative Results for USP Method 1 and Method 2*

Drug 1	Drug 2	USP <788> Method 1						USP <788> Method 2		
		LO 10+	LO 25+	LO Result	FI 10+	FI 25+	FI Result	BMI 10+	BMI 25+	BMI Result
Cisatracurium 2 mg/mL	Alprostadil 20 mcg/mL in D5W	11 ± 4	0 ± 1	C	38 ± 16	2 ± 3	I	5 ± 25	1 ± 5	C
Cisatracurium 2 mg/mL	Ketamine 10 mg/mL	43 ± 5	1 ± 1	I	130 ± 28	2 ± 3	I	166 ± 23	10 ± 8	I
Cisatracurium 2 mg/mL	Ampicillin 30 mg/mL in NS	11 ± 8	0 ± 0	C	101 ± 25	9 ± 7	I	95 ± 106	1 ± 34	I
Cisatracurium 2 mg/mL	Vasopressin 1 u/mL in D5W	5 ± 1	0 ± 0	C	36 ± 22	1 ± 3	I	0 ± 15	1 ± 11	C
Cisatracurium 2 mg/mL	Bumetanide 0.25 mg/mL	1 ± 2	0 ± 1	C	15 ± 17	1 ± 2	C	8 ± 14	1 ± 16	C
Milrinone 200 mcg/mL	Alprostadil 20 mcg/mL in D5W	4 ± 2	1 ± 1	C	72 ± 22	7 ± 5	I	13 ± 24	22 ± 80	I
Hydromorphone 0.5 mg/mL in D5W	Bumetanide 0.25 mg/mL	2 ± 1	0 ± 0	C	36 ± 19	4 ± 5	I	30 ± 23	0 ± 3	I
Dexmedetomidine 4 mcg/mL	Ketamine 10 mg/mL	82 ± 6	0 ± 0	I	79 ± 20	4 ± 3	I	139 ± 25	12 ± 10	I
Dexmedetomidine 4 mcg/mL	Bumetanide 0.25 mg/mL	4 ± 2	0 ± 0	C	38 ± 20	4 ± 5	I	1 ± 9	2 ± 10	C
Ampicillin/ sulbactam 20 mg/mL in NS	Heparin 500 u/mL in NS	15 ± 4	0 ± 1	C	18 ± 11	0 ± 0	C	7 ± 28	2 ± 13	C
Ampicillin/ sulbactam 20 mg/mL in NS	Bumetanide 0.25 mg/mL	5 ± 1	0 ± 0	C	15 ± 9	0 ± 0	C	1 ± 19	1 ± 10	C
Rocuronium 10 mg/mL	Hydromorphone 0.5 mg/mL in D5W	0 ± 1	0 ± 0	C	34 ± 10	4 ± 5	I	6 ± 8	0 ± 4	C
Rocuronium 10 mg/mL	Dexmedetomidine 4 mcg/mL	2 ± 1	0 ± 0	C	48 ± 11	1 ± 3	I	0 ± 10	0 ± 4	C
Rocuronium 10 mg/mL	Ketamine 10 mg/mL	57 ± 4	0 ± 1	I	90 ± 46	0 ± 0	I	139 ± 24	7 ± 8	I
Rocuronium 10 mg/mL	Vasopressin 1 u/mL in D5W	6 ± 1	0 ± 0	C	18 ± 14	1 ± 2	C	3 ± 14	1 ± 10	C
Rocuronium 10 mg/mL	Bumetanide 0.25 mg/mL	1 ± 1	0 ± 0	C	51 ± 14	7 ± 7	I	14 ± 22	1 ± 7	I
Bumetanide 0.25 mg/mL	Alprostadil 20 mcg/ml in D5W	4 ± 2	0 ± 0	C	14 ± 7	1 ± 2	C	5 ± 14	1 ± 8	C
Bumetanide 0.25 mg/mL	Sildenafil 0.8 mg/mL	1 ± 1	1 ± 1	C	23 ± 21	6 ± 9	I	146 ± 189	16 ± 10	I
Bumetanide 0.25 mg/mL	Ampicillin 30 mg/mL in NS	4 ± 1	0 ± 1	C	33 ± 12	0 ± 0	I	0 ± 17	0 ± 5	C
Bumetanide 0.25 mg/mL	Heparin 500 u/mL in NS	25 ± 6	0 ± 0	C	54 ± 20	2 ± 3	I	10 ± 16	1 ± 8	C

Table 2. USP <788> Drug-Drug Combination Cumulative Results for USP Method 1 and Method 2* *cont*

Bumetanide 0.25 mg/mL	Epinephrine 100 mcg/mL	5 ± 2	0 ± 0	C	100 ± 12	10 ± 5	I	56 ± 22	2 ± 6	I
Bumetanide 0.25 mg/mL	Calcium chloride 100 mg/mL	15 ± 9	0 ± 1	C	7 ± 6	0 ± 0	C	134 ± 125	6 ± 16	I
Vancomycin 5 mg/mL in NS	Ceftriaxone 40 mg/mL in D5W	2 ± 1	0 ± 0	C	26 ± 14	1 ± 2	I	28 ± 25	2 ± 8	I
Vancomycin 5 mg/mL in NS	Cefepime 40 mg/mL in NS	30 ± 10	0 ± 0	I	691 ± 51	47 ± 13	I	258 ± 43	17 ± 13	I
Vancomycin 5 mg/mL in NS	Lacosamide 10 mg/mL	4 ± 1	0 ± 0	C	27 ± 11	3 ± 5	I	16 ± 19	1 ± 4	I
Calcium chloride 100 mg/mL	D20 1/2 NS with 20 mEq/L KCl	1 ± 1	0 ± 0	C	14 ± 7	0 ± 0	C	36 ± 28	0 ± 7	I
Dihydroergotamine 4 mcg/mL in NS	D5WNS with 20 mEq/L KCl	3 ± 1	0 ± 0	C	52 ± 17	3 ± 3	I	30 ± 11	6 ± 2	I
Dihydroergotamine 4 mcg/mL in NS	Ondansetron 2 mg/mL	10 ± 5	0 ± 0	C	51 ± 29	2 ± 3	I	29 ± 15	9 ± 6	I
Ceftriaxone 40 mg/mL in D5W	Lactated Ringer's	1 ± 1	0 ± 0	C	27 ± 13	1 ± 3	I	15 ± 20	2 ± 5	I

10+ and 25+, particles over 10 and 25 µm in size, respectively; BMI, backgrounded membrane imaging; C, compatible; D5W, 5% dextrose in water; FI, flow imaging; I, incompatible; KCl, potassium chloride; LO, light obscuration; NS, normal saline; USP Methods 1 and 2, see text for details.

* Compatible per USP <788>, but incompatible by FlowCam imaging. Numeric data are presented as particles per milliliter, mean ± SD.

and the sizing bin settings on the instrument were set to ≥2, ≥5, ≥10, and ≥25 µm. A standard water wash protocol was used after each measurement to clean the instrument, and the number of microparticles measured in "particle-free" water before each subsequent run was less than 10 particles/mL. For each sample, the average particle count was calculated from the values from 4 measurements for at total analyzed volume of 4 mL of each sample.

Subvisible Particle Analysis via BMI. Subvisible particle analysis was performed using the Horizon Subvisible Particle Analysis Instrument (Halo Labs). For each measurement, each filter was rinsed with 50 µL of particle free water and then 500 µL of sample pipetted onto the 0.4-µm filter membrane specific to this instrument. The filter was dried, washed with 500 µL of particle free water, dried, and analyzed. Each set of images were then analyzed for dust contamination, and these particles were manually removed from the final particle counts. Each measurement was multiplied by 1.587 to correct for the area of the filter disk not physically counted. For each sample, the average particle count was calculated from the values from 6 measurements for a total analyzed volume of 3 mL of each sample.

Determination of Compatibility. USP <788> method 1 and 2 were both used to determine compatibility. USP <788> Method 1 assessments were performed using LO.[18] Flow imaging results were assessed using USP <788> method 1 criteria, and BMI results were assessed using USP <788> method 2 criteria. For this evaluation, the particles per milliliter count specified in USP <788> for large volume parenterals were used for all samples. For FI and LO methods, the combination was considered compatible if the total count of particles greater than or equal to 10 µm did not exceed 25 particles/mL and the total count of particles greater than or equal to 25 µm did not exceed 3 particles/mL. Combinations evaluated with BMI were considered physically compatible if they fell within the USP <788> particle count limits of less than or equal to 12 particles/mL >10 µm, and less than or equal to 2 particles/mL over 25 µm.[10]

Results

Twenty-nine different combinations of medications were tested. None of the samples tested required further dilution for particle counting on any of the instruments. Particle counts for each combination and method are reported in Tables 2 and 3. None of the samples analyzed met criteria for incompatibility based on visual inspection. The pH measurements for all samples did not vary between timepoints. No color change or gas formation was noted on visual inspection.

Five combinations met the criteria for compatibility across all 3 instrumental methods. These combinations included the following: 1) cisatracurium 2 mg/mL with bumetanide 0.25 mg/mL; 2) ampicillin/sulbactam 20

Table 3. Drug-Drug Combinations by Compatibility

Drug 1	Drug 2	LO Result	FI Result	BMI Result	Author Recommendations
Compatible by all instruments					
Cisatracurium 2 mg/mL	Bumetanide 0.25 mg/mL	C	C	C	Compatible at Y-site
Ampicillin/sulbactam 20 mg/mL in NS	Heparin 500 u/mL in NS	C	C	C	
Ampicillin/sulbactam 20 mg/mL in NS	Bumetanide 0.25 mg/mL	C	C	C	
Rocuronium 10 mg/mL	Vasopressin 1 u/mL in D5W	C	C	C	
Bumetanide 0.25 mg/mL	Alprostadil 20 mcg/ml in D5W	C	C	C	
Incompatible by all instruments					
Cisatracurium 2 mg/mL	Ketamine 10 mg/mL	I	I	I	Incompatible at Y-site
Dexmedetomidine 4 mcg/mL	Ketamine 10 mg/mL	I	I	I	
Rocuronium 10 mg/mL	Ketamine 10 mg/mL	I	I	I	
Vancomycin 5 mg/mL in NS	Cefepime 40 mg/mL in NS	I	I	I	
Incompatible by 2 instruments, compatible by 1					
Cisatracurium 2 mg/mL	Ampicillin 30 mg/mL in NS	C	I	I	High risk of being incompatible at Y-site, not recommended to infuse together
Milrinone 200 mcg/mL	Alprostadil 20 mcg/mL in D5W	C	I	I	
Hydromorphone 0.5 mg/mL in D5W	Bumetanide 0.25 mg/mL	C	I	I	
Rocuronium 10 mg/mL	Bumetanide 0.25 mg/mL	C	I	I	
Bumetanide 0.25 mg/mL	Sildenafil 0.8 mg/mL	C	I	I	
Bumetanide 0.25 mg/mL	Epinephrine 100 mcg/mL	C	I	I	
Vancomycin 5 mg/mL in NS	Ceftriaxone 40 mg/mL in D5W	C	I	I	
Vancomycin 5 mg/mL in NS	Lacosamide 10 mg/mL	C	I	I	
Dihydroergotamine 4 mcg/mL in NS	D5WNS with 20 mEq/L KCl	C	I	I	
Dihydroergotamine 4 mcg/mL in NS	Ondansetron 2 mg/mL	C	I	I	
Ceftriaxone 40 mg/mL in D5W	Lactated Ringer's	C	I	I	
Incompatible by 1 instrument, Compatible by 2					
Cisatracurium 2 mg/mL	Alprostadil 20 mcg/mL in D5W	C	I	C	Inconclusive. Data are inconsistent but evidence of potential incompatibility exists. Avoid co-infusion of these combinations at Y-site whenever possible.
Cisatracurium 2 mg/mL	Vasopressin 1 u/mL in D5W	C	I	C	
Dexmedetomidine 4 mcg/mL	Bumetanide 0.25 mg/mL	C	I	C	
Rocuronium 10 mg/mL	Hydromorphone 0.5 mg/mL in D5W	C	I	C	
Rocuronium 10 mg/mL		C	I	C	
Bumetanide 0.25 mg/mL	Dexmedetomidine 4 mcg/mL	C	I	C	
Bumetanide 0.25 mg/mL	Ampicillin 30 mg/mL in NS	C	I	C	
Bumetanide 0.25 mg/mL	Heparin 500 u/mL in NS	C	C	I	
Calcium chloride 100 mg/mL	Calcium chloride 100 mg/mL D20 1/2 NS with 20 mEq/L KCl	C	C	I	

BMI, backgrounded membrane imaging; C, compatible; D5W, 5% dextrose in water; FI, flow imaging; I, incompatible; KCl, potassium chloride; LO, light obscuration; NS, normal saline

mg/mL in normal saline (NS) with heparin 500 unit/mL in NS; 3) ampicillin/sulbactam 20 mg/mL in NS with bumetanide 0.25 mg/mL; 4) rocuronium 10 mg/mL with vasopressin 1 unit/mL; and 5) bumetanide 0.25 mg/mL with alprostadil 20 mcg/mL in 5% dextrose in water (D5W). The remaining 24 combinations reached the threshold to be considered incompatible by at least 1 of the 3 instrumental methods. The combinations that met criteria for incompatibility across all 3 methods were cisatracurium 2 mg/mL with ketamine 10 mg/mL, dexmedetomidine 4 mcg/mL with ketamine 10 mg/mL, rocuronium 10 mg/mL with ketamine 10 mg/mL, and vancomycin 5 mg/mL in NS with cefepime 40 mg/mL in NS. Results are compiled in Table 3 with author recommendations.

Light obscuration identified 4 of the 29 (14%) combinations as incompatible. Subvisible particle analysis via BMI identified physical incompatibility in 59% of combinations (17 of 29). Flow imaging identified 76% of combinations tested (22 of 29) as incompatible. All of the samples deemed incompatible by LO were also found to be incompatible by the other 2 methods as well. Flow imaging and BMI results agreed in 20 of the 29 samples tested (69%).

Discussion

USP <788> methods 1 and 2 were both evaluated in this study to ensure accuracy in the findings. Flow imaging was used in conjunction with LO to assess combinations using USP <788> method 1 criteria, while

USP <788> method 2 criteria were assessed using BMI. Notably, FI and BMI are not specifically recommended by USP <788>. There are inconsistent results between methods, which presents a conundrum regarding the optimal method for evaluation, and each method presents limitations. However, the combination of all data has shed light on particle levels that would be infused into patients.

In the United States, USP <788> is the governing standard to address physical stability and particulate thresholds for aqueous parenterally delivered medications. The recommended threshold for small volume parenteral products (less than 100 mL) lists the acceptable particle count to be less than or equal to 6000 or 3000 particles greater than or equal to 10 µm in methods 1 and 2, respectively, and less than 600 or 300 particles greater than or equal to 25 µm per container. However, for large volume parenterals (greater than 100 mL volume) the particles per container thresholds were changed to be particle per milliliter thresholds.[10] Importantly, using USP <788> method 1 criteria, a 99-mL container of a medication would be allowed to have 6000 particles of ≥10 µm in diameter, whereas a 101-mL container would have a limit of only 2525 particles of the same size. A similar phenomenon occurs when applying method 2 thresholds to the same samples. If we were to follow USP <788> particle limits for small volume parenterals, the majority of the data presented here could be considered "compatible." However, there is concern that the standards presented in the USP <788> may not be conservative enough to protect neonatal and pediatric patients. Supporting data for these USP <788> thresholds could not be found, and thus use of the more stringent particle per milliliter thresholds were used in this study.

The rationale for the application of particle per milliliter thresholds in this evaluation is multifaceted. Pediatric patients require weight-based dosing, which leads to the significant volume variation of each patient-specific dose. It is rare that a pediatric patient would receive an entire container of a manufacturer-supplied medication. Additionally, the clinical effect of the total particle exposure by weight of a 10-mL vial of a medication is significantly different in a patient that weighs 0.7 kg compared with a 70-kg adult. There are safety concerns related to the ability of premature neonates to process particulates in solutions as efficiently as adults, and the particle per milliliter counts are more stringent when applied to smaller volume infusions. To be able to accurately compare the exposure of patients with weights that range from 0.5 kg to 100 kg accurately, a unifying denominator such as mL is required for clinical interpretation.

Particles in high quantities or those with large diameters have the potential to be more devastating in small infants and children compared with adults, due to smaller pulmonary capillary size and relatively large fluid intake relative to their body weight.[23,24] Because of the administration challenges specific to pediatric patients and the clinical risk associated with particle infusions, FI and BMI instrumental methodologies were used to assess USP <788> methods 1 and 2, despite a lack of precedent for either method in USP <788> guidelines. In this evaluation, these 2 methods demonstrated much higher accuracy for identifying particulates in solution when compared with LO.

Medication administration challenges in pediatric patients are numerous. Specific to this study, the slow rate of infusion necessitated by dosing in infants and children can lead to a prolonged exposure time of medications to each other in the tubing prior to reaching the patient. In 1 evaluation of in-line filters following 72 hours of use in 9 different patients in a pediatric intensive care unit, the majority of particles identified were between 5 and 50 µm in diameter.[9] The capillary diameter in lung tissue of infants and children is thought to be somewhere between 5 and 9 µm.[23] Five to 9-µm particle thresholds are not addressed by USP <788> and thus are not reported in this evaluation. However, it is worth noting that these particles may have the potential to cause harm when infused into pediatric patients.

Additionally, infusion of large particles may cause physical obstruction, a theory that is supported by research performed by Puntis et al[24] demonstrating that particles in parenteral nutrition were implicated in the formation of granulomatosis arteritis in 73 infants. Due to the risk of multisystem organ failure, systemic inflammatory response syndrome, pulmonary toxicity, and even death related to incompatible medications being infused together, it is advisable to use caution when assessing compatibilities for a clinical setting. Incorporation of more sensitive analysis methods such as FI and BMI may be more appropriate to accurately determine physical compatibility.

However, it is worth noting the sometimes inconsistent results between LO, FI, and BMI technologies that were identified in this study. One notable inconsistency of these data is the instances in which higher particle counts were identified using BMI when compared with FI or LO. For medications mixed with higher dextrose containing fluids (15% dextrose containing solutions and above), this may be explained by the refractive index of the solution, leading to a failure to detect particles using method 1 instruments like FI and LO.[25] For dextrose-free combinations and those with lower dextrose percentages, particles might break apart due to the turbulence of fluid being pulled through the flowcells for FI and LO compared with the relatively gentle application process of plating samples onto filter disks used with BMI.

Another inconsistency found in these data is in specific samples in which testing using LO or FI demonstrated a higher particle count when compared with BMI. One theory behind this discrepancy may be related to silicone oil particles passing easily through the membrane filters used for BMI, as demonstrated by Helbig et al.[26] Despite digital filter-based corrections for silicone oil counts with

FI results, some silicone oil droplets may remain present in the FI data, and corrections for silicone oil are not available for LO data.

Additionally, simulated Y-site compatibility testing using a 1:1 mixture within a syringe does not account for physicochemical interactions that may occur during actual IV administration, including interactions between the medication and the IV tubing. Recent publications have demonstrated a difference in physical drug compatibilities in simulated Y-site testing compared with actual Y-site compatibility testing.[27] This is a limitation of this evaluation, and in the future warrants actual Y-site evaluation to determine compatibility while considering interactions between the IV tubing and the medications evaluated. An additional limitation of this evaluation is that chemical compatibility testing was not performed.

A final limitation of this study relates to standard pediatric continuous infusion concentrations. Most medications tested in this study comply with the American Society of Health-System Pharmacists recommendations, however the concentrations tested for alprostadil, heparin, and epinephrine were more concentrated than recommended for pediatric patients.[28] These concentrations were selected based on the highest-possible concentration available at the study institution to support clinically appropriate extrapolation to concentrations lower than those reported.

Applying USP <788> methods clinically to pediatric pharmacy practice brings to light clinical and analytical controversies. Are current LO and microscopy methods the most appropriate to use to test the compatibility of medication combinations? Additionally, are the current USP <788> particle count thresholds still applicable given the increased particle detection rates of instrumental methods now available? The USP chapter offers no explanation as to where the existing particle count thresholds originated, why method 1 has particle count limits that are essentially double that of method 2, or why large volume parenterals are held to a different standard when compared with small volume parenterals. Regardless, we feel that results of incompatibility from any method used should preclude clinical use of a medicine combination for all patients, and for neonates and small infants in particular.

This report evaluated medication combinations at specific concentrations used for pediatric patients. Although any incompatibility noted in our evaluation would likely suggest a similar physical incompatibility in clinical practice, it is difficult to fully extrapolate this laboratory-based data to the clinic without further chemical compatibility testing. However, knowledge of physical compatibilities of these medications is a step forward in improving clinical outcomes and reducing IV access requirements in pediatric patients.

Article Information

Affiliations. Department of Pharmacy (ELR, KP, AS), Children's Hospital Colorado, Aurora, CO; Departments of Basic Science (CH, JFC), Pharmacy (JB), University of Colorado Skaggs School of Pharmacy and Pharmaceutical Science, Aurora, CO.

Correspondence. Emma L. Ross, PharmD; emma.ross@childrenscolorado.org

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

Acknowledgments. The authors thank Children's Hospital Colorado Department of Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Science, and Halo Labs for donating materials to make this research possible.

Submitted. August 11, 2021

Accepted. February 10, 2022

References

1. Kumar P, Walker JK, Hurt KM, et al. Medication use in the neonatal intensive care unit: current patterns and off-label use of parenteral medications. *J Pediatr*. 2008;152(3):412–415.
2. Burny I, Lieh-Lai MW, Gaynor K, Thomas RL. Patterns of medication use and errors in a pediatric intensive care unit. *Pediatr Crit Care Med*. 2004;5(5):510.
3. Perez M, Décaudin B, Maiguy-Foinard A, et al. Dynamic image analysis to evaluate subvisible particles during continuous drug infusion in a neonatal intensive care unit. *Sci Rep*. 2017;7(1):9404.
4. Lehr HA, Brunner J, Rangoonwala R, Kirkpatrick CJ. Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle. *Am J Respir Crit Care Med*. 2002;165(4):514–520.
5. Bradley JS, Wassel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics*. 2009;123(4):609–613.
6. Benlabed M, Perez M, Gaudy R, et al. Clinical implications of intravenous drug incompatibilities in critically ill patients. *Anaesth Crit Care Pain Med*. 2019;38(2):173–180.
7. Arima H, Hirate H, Sugiura T, et al. IV injection of polystyrene beads for mouse model of sepsis causes severe glomerular injury. *J Intensive Care*. 2014;2(1):21.

8. Robinson LA, Braimbridge MV, Hearse DJ. Impairment of myocardial function induced by particulate contamination of cardioplegic solutions. *Adv Myocardiol*. 1985;6:503–512.
9. Jack T, Brent BE, Boehne M, et al. Analysis of particulate contaminations of infusion solutions in a pediatric intensive care unit. *Intensive Care Med*. 2010;36(4):707–711.
10. United States Pharmacopeia and the National Formulary. <788> Particulate matter in injections. United States Pharmacopeial Convention; Accessed September 27, 2018. www.uspfn.com/sites/default/files/usp_pdf/EN/USPNF/788ParticulateMatter.pdf
11. Vargas SK, Eskafi A, Carter E, Ciaccio N. A comparison of background membrane imaging versus flow technologies for subvisible particle analysis of biologics. *Int J Pharm*. 2020;578:119072.
12. Corvari V, Narhi LO, Spitznagel TM, et al. Subvisible (2-100 µm) particle analysis during biotherapeutic drug product development: part 2, experience with the application of subvisible particle analysis. *Biologicals*. 2015;43(6):457–473.
13. Matter A, Koulov A, Singh S, et al. Variance between different light obscuration and flow imaging microscopy instruments and the impact of instrument calibration. *J Pharm Sci*. 2019;108(7):2397–2405.
14. Scott-Warren VL, Morley RB. Pediatric vascular access. *BJA Education*. 2015;15(4):199–206.
15. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections, 2011. Accessed September 27, 2018. https://www.cdc.gov/hai/pdfs/bsi-guidelines-2011.pdf
16. Alexandrou E, Ramjan LM, Spencer T, et al. The use of midline catheters in the adult acute care setting—clinical implications and recommendations for practice. *J Assoc Vasc Access*. 2011;16:35–41.
17. Banton J, Leahy-Gross K. Assessing catheter performance: four years of tracking patient outcomes of midline, midclavicular and PICC line program. *J Assoc Vasc Access*. 1998;3:19–25.
18. Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters. A randomized controlled trial. *Ann Intern Med*. 1991;114(10):845–854.
19. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006;81(9):1159–1171.
20. Pittiruti M, Hamilton H, Biffi R, et al; ESPEN. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr*. 2009;28(4):365–377.
21. Barczykowska E, Szwed-Kolińska M, Wróbel-Bania A, Ślusarz R. The use of central venous lines in the treatment of chronically ill children. *Adv Clin Exp Med*. 2014;23(6):1001–1009.
22. Trissel's 2 clinical pharmaceutics database: parenteral compatibility. Lexicomp. Wolters Kluwer Health, Inc. Accessed July 30, 2021. https://online.lexi.com/lco/action/ivcompatibility/trissels
23. Good M, Kolls JK, Empey KM. Neonatal pulmonary host defense. In Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology*. Vol. 2, 5th ed. Elsevier Health Sciences; 2017: 1262-1293.
24. Puntis JW, Wilkins KM, Ball PA, et al. Hazards of parenteral treatment: do particles count? *Arch Dis Child*. 1992;67(12):1475–1477.
25. Zölls S, Gregoritza M, Tantipolphan R, et al. How subvisible particles become invisible-relevance of the refractive index for protein particle analysis. *J Pharm Sci*. 2013;102(5):1434–1446.
26. Helbig C, Ammann G, Menzen T, et al. Backgrounded membrane imaging (BMI) for high-throughput characterization of subvisible particles during biopharmaceutical drug product development. *J Pharm Sci*. 2020;109(1):264–276.
27. Kufel WD, Miller CD, Johnson PR, et al. Y-site incompatibility between premix concentrations of vancomycin and piperacillin-tazobactam: do current compatibility testing methodologies tell the whole story? *Hosp Pharm*. 2017;52(2):132–137.
28. American Society of Health-System Pharmacists (ASHP). Standardize 4 safety: pediatric continuous infusion standard. 2020. Accessed February 9, 2022. https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Pediatric-Infusion-Standards.pdf