ADULT CONTINUOUS INFUSION STANDARDS

STANDARDIZE 4 SAFETY INITIATIVE

Standardize 4 Safety is the first national, interprofessional effort to standardize medication concentrations to reduce errors, especially during transitions of care.

These national standards will cover:

- Concentrations and dosing units for intravenous continuous medications for adult patients.
- Concentrations for compounded oral liquid medications.
- Concentrations and dosing units for intravenous continuous medications for pediatric patients.
- Doses for oral liquid medications.
- Concentrations for intravenous intermittent medications.
- Concentrations for PCA and epidural medications.

The Standardize 4 Safety initiative began in 2008 when a multi-stakeholder IV summit was held to address preventing patient harm and death from intravenous (IV) medication errors. Among the recommendations made by the participants was to establish national standards for IV medications in hospitals including standardized concentrations and dosing. In addition, it was recommended that the national standards be created in collaboration with the Food and Drug Administration (FDA), the pharmaceutical industry, and other stakeholders. Since the summit, establishing standardized concentrations has garnered strong support from ASHP members, the Joint Commission, the Institute for Safe Medical Practices (ISMP), and others. [1] [2] [3] [4] [5]

In 2015 the FDA, through its Safe Use Initiative, awarded ASHP a grant to develop and implement national standardized concentrations for IV and oral liquid medications. The aims of the grant were to: (1) identify a nationwide expert interprofessional panel consisting of physicians, nurses, and pharmacists; (2) create standards for adult continuous IV infusions, compounded oral liquid medications, pediatric continuous IV infusions, doses for liquid medications, intravenous intermittent infusions, and PCA and epidural medications; (3) disseminate the standards and assess their adoption.

1 ASHP Best Practices: Position and guidance documents of ASHP. 2014. ASHP, Bethesda, Maryland.

2 ISMP. Standard Concentrations of Neonatal Drug Infusions. 2011. https://www.ismp.org/recommendations/standard-concentrations-neonatal-drug-infusions. (accessed September 20, 2020)

3 Larsen GY, Parker HB, Cash J. et.al. Standard Drug Concentrations and Smart-Pump Technology Reduce Continuous-Medication-Infusion Errors in Pediatric Patients. Pediatrics 2005;116:e21–e25.

4 Joint Commission. New and Revised Standards for Pediatric Population Improvement Initiative. 2011. https://www.jointcommission.org/-/media/deprecated-unorganized/imported-assets/tjc/system-folders/assetmanager/ped_field_reviewpdf.pdf?db=web&hash=670BC65546F15F2D1D643263E0C85648. (accessed September 20, 2020)

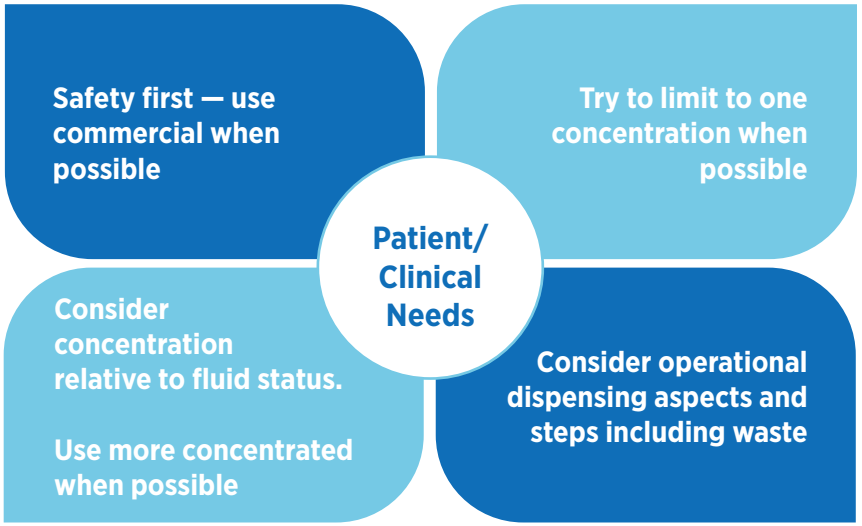
5 Shekelle PG, Wachter RM, Pronovost PJ, et.al. An Updated Critical Analysis of the Evidence for Patient Safety Practices. Comparative Effectiveness Review No. 211. (Prepared by the Southern California-RAND Evidence-based Practice Center under Contract No. 290-2007-10062-I.) AHRQ Publication No. 13-E001-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2013. www.ahrq.gov/research/findings/evidence-based-reports/ptsafetyuptp.html. (accessed September 20, 2020)

Funded by FDA Safe Use Initiative.

WHY STANDARDIZE

To Err is Human was published in 1999 and highlighted the harm to patients from healthcare error. In that report, medication errors were stated to be responsible for one of 131 outpatient and one of 854 inpatient deaths.[6] Healthcare continues to struggle to eliminate harm to patients. A systematic review and meta-analysis in 2019 estimated one in 20 patients are exposed to preventable medical harm with the highest incidence of events due to medications. Compounded medications,[7] especially those given intravenously, are known to be high risk for error due to added complexity and multiple steps required for determining dosing when ordering, concentrations for preparation and rates of infusion for administering.[8] [9] Using standardization as a quality improvement tool decreases variation, improves safety, and is the foundation for using clinical pathways and evidence-based guidelines. Standardization allows providers to manage excessive and unintended variation as they customize care for patients.[10]

PRINCIPLES FOR ADULT CONTINUOUS INFUSION STANDARDS



6 Kohn LT, Corrigan J, Donaldson Molla S, eds; Institute of Medicine Committee on Quality of Health Care in America. To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 2000.

7 Panagioti, M, Khan K, Keers RN, et.al. Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis. BMJ 2019;366:l4185 | doi: 10.1136/bmj.l4185.

8 Hedlund N, Beer I, Hoppe-Tichy T, Trbovich P. Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings. BMJ Open. 2017; 7(12): e015912.

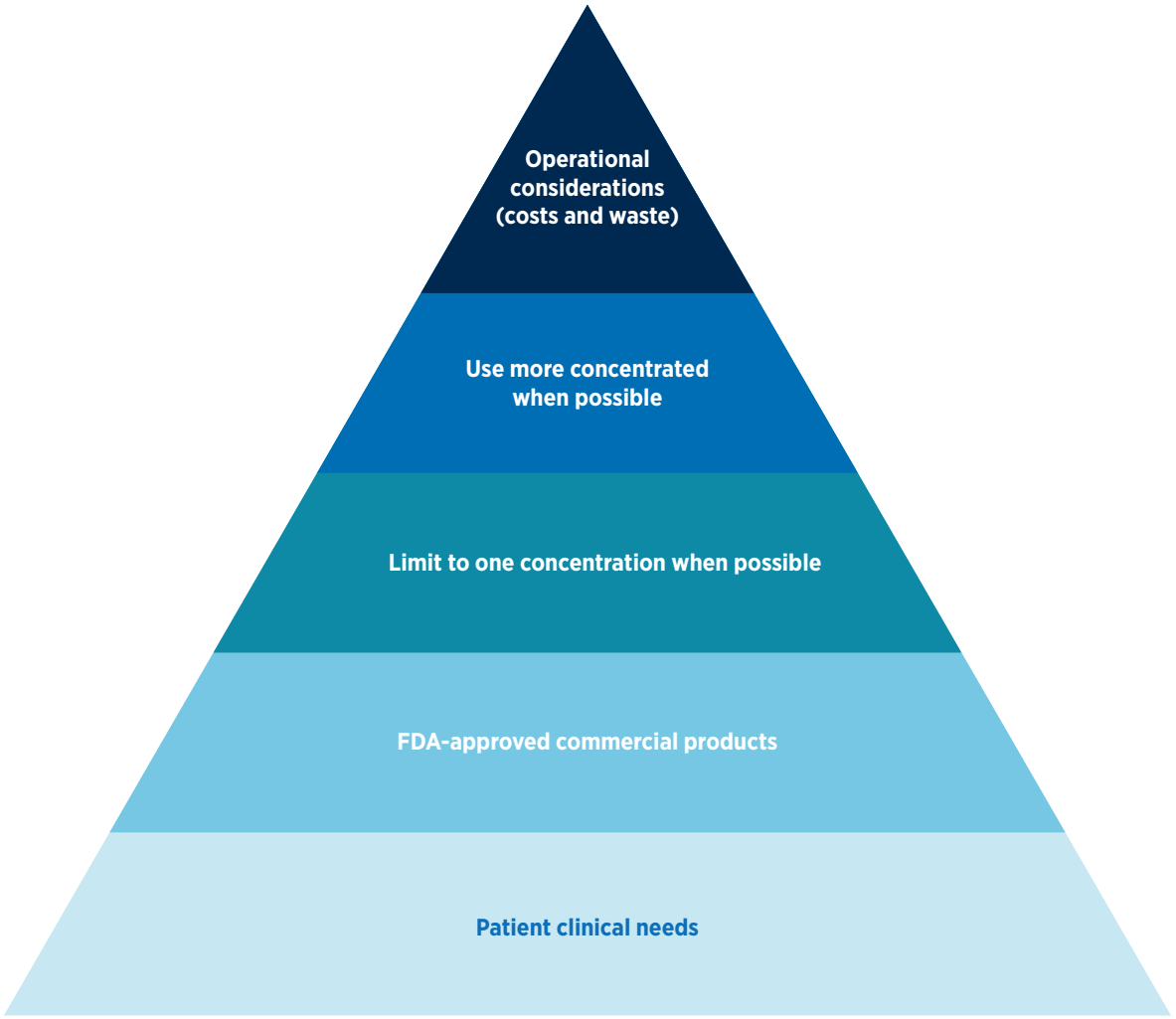
9 Sutherland A, Canobbio M, Clarke J, et.al. Incidence and prevalence of intravenous medication errors in the UK: a systematic review. Eur J Hosp Pharm. 2020 Jan; 27(1): 3–8.

10 Lloyd R. Does Standardization Mean the End of Autonomy? Institute for Healthcare Improvement. http://www.ihi.org/communities/blogs/does-standardization-mean-the-end-of-autonomy. (accessed September 15, 2020.

HOW THE NATIONAL MEDICATION CONCENTRATION STANDARDS WERE DEVELOPED

A comprehensive environmental scan was conducted to identify the appropriate medications to be addressed in the respective standard concentrations. A multi-disciplinary expert panel was convened for each standard concentration category. Members were selected based on their expertise in the subject matter and identified with assistance from organizations such as The American Society of Anesthesiologists, Society of Critical Care Medicine, and American Association of Critical-Care Nurses. Each expert panel was charged to establish standard principles to guide their decisions in creating the respective standard concentration recommendations. Once a draft of standards was established, it was released for public comment and review by ASHP staff and ISMP. The expert panel subsequently met to address all comments and generate the National Medication Concentration Standards.

PRINCIPLES FOR EXPERT PANEL DELIBERATIONS



EXPERT PANEL

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DISCLAIMERS

- Suggested concentrations may differ from the package insert (PI) information for a drug. This is due to clinical needs that may have transpired postmarket. When this is the case, studies are available to support the use of a concentration different than what the parent company originally pursued through the new drug application (NDA) process.
- Please use the utmost caution when using a concentration different than the PI, especially if rate information is used from the PI.
- Dosing units were derived from PI information, commonly used drug-reference guides, and clinical practice guidelines.
- Of special note, the expert panel is recommending that weight-based dosing be used for vasopressors (i.e., per kg, per minute), which may differ from institution specific guidelines. We strongly encourage that drug libraries and electronic health records (EHRs), including the electronic medication administration record, make distinct differences for weight-based vs. non-weight-based dosing so nurses can easily distinguish what pump programming is needed.
- These concentrations are guidelines only and are not mandatory. It is our hope that organizations will voluntarily adopt these concentrations and join a national movement to use standardization across the care continuum as an error-prevention strategy for patient safety.
- The information contained in this table is subject to the professional judgment and interpretation of the practitioner. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised that ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the self-assessment tool. Any user of the table is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in it, and will bear no responsibility or liability for the results or consequences of its use.

CONSIDERATIONS IN USING THE ADULT CONTINUOUS INFUSION STANDARDS

The 80/20 rule was applied by the expert panel to determine recommended standard concentrations. The concentrations listed reflect those applicable to most patient care circumstances. The panel recognizes situations occur where the most appropriate concentration for a patient may not be the recommended standard.

Whenever possible one standard infusion concentration is the recommendation. When more than one standard concentration was recommended it was to accommodate patient care needs for fluid restrictions, differences required for peripheral versus central lines, to simplify calculations and accommodate limitations of pump infusion rates.

Medications with more than one recommended concentration are listed from lowest to highest concentration, with the numbering corresponding to the respective stability reference(s).

Drug	Concentration Standards	Dosing units	Commercially available	References
Alteplase	1 mg/mL	mg/hour	Yes, comes in a kit with diluent	1. Frazen BS, Maximal Dilution of Activase. Am J Hosp Pharm, 1990;47:2016. Product Information: Activase(R) intravenous injection, alteplase intravenous injection. Genentech, Inc.(per Manufacturer), South San Francisco, CA, 2015
Amiodarone	1. 1.8 mg/mL 2. 3.6 mg/mL	mg/min	Yes	1. Product Information: amiodarone HCl intravenous injection, amiodarone HCl intravenous injection. Teva Canada Limited (per Health Canada), Toronto, ON, Canada, 2016. - 2. Product Information: amiodarone HCl intravenous injection, amiodarone HCl intravenous injection. Teva Canada Limited (per Health Canada), Toronto, ON, Canada, 2016.
Argatroban	1 mg/mL	**mcg/kg/min***	Yes	1. Product Information: argatroban injection, argatroban injection. GlaxoSmithKline, Research Triangle Park, NC, 2009. Product Information: argatroban IV injection aqueous solution, argatroban IV injection aqueous solution. The Medicines Company (per DailyMed), Parsippany, NJ, 2011.
Bumetanide	0.25 mg/mL	mg/hour	Administer undiluted	1. Roche Laboratories. Bumex® (bumetanide) tablets and injection prescribing information. Nutley, NJ; 1999 Feb.
Cisatracurium[1 2]	2 mg/mL	**mcg/kg/min***	Administer undiluted	1. Abbvie. Nimbex® (cisatracurium besylate) injection prescribing information. North Chicago, IL; 2016 Dec.
Dexmedetomidine	4 mcg/mL	mcg/kg/hour	Yes	1. Hospira. Precedex® (dexmedetomidine) injection prescribing information. Lake Forest, IL; 2016 Apr.
Dil**TIAZ**em	1 mg/mL	mg/hour	No	1. Diltiazem HCL 0.5% intravenous injection, Akor, Inc. (per DailyMed) Lke Forest, IL. 2012.
DOBUTamine	4000 mcg/mL	mcg/kg/min	Yes	1. Hospira. Dobutamine in 5% dextrose injection prescribing information. Lake Forest, IL; 2006 June.
DOPamine[3]	1. 1600 mcg/mL 2. 3200 mcg/mL	mcg/kg/min	Yes	1. Hospira. Dopamine hydrochloride and 5% dextrose injection prescribing information. Lake Forest, IL; 2014 May. 2. Hospira. Dopamine hydrochloride and 5% dextrose injection prescribing information. Lake Forest, IL; 2014 May.

Drug	Concentration Standards	Dosing units	Commercially available	References
EPINEPHrine[4]	1. 20 mcg/mL 2. 40 mcg/mL	mcg/kg/min	No	1a. Allwood MD. The stability of four catecholamines in 5% glucose infusions. J Clin Pharm Ther. 1991:16:337-40. 1b. VanMatre ET, Ho KC, Lyda C, et.al. Extended Stability of Epinephrine Hydrochloride Injection in Polyvinyl Chloride Bags Stared in Amber Ultraviolet Light-Blocking Bags. Hospital Pharmacy. 2017;52:570-573. 2a. Carr RR, Decarie D, EnsomMHH. Stability of Epinephrine at Standard Concentrations. Can J Hosp Pharm. 2014;67:197-202 2b. Peddicord TE, Olsen KM, ZumBrunnen TL, et.al. Stability of high-concentration dopamine hydrochloride, norepinephrine bitartrate, epinephrine hydrochloride and nitroglycerin 5% dextrose injetion. Am J Health-Syst Pharm. 1997;54:1417-19.
Esmolol	1. 10 mg/mL 2. 20 mg/mL	mcg/kg/min	Yes	1. Baxter. Brevibloc® injection (esmolol hydrochloride) prescribing information. (dated 1998 Jun). In: Physicians' desk reference. 54th ed. Montvale NJ: Medical Economics Company Inc; 2000:655-7. 2. Baxter. Brevibloc® injection (esmolol hydrochloride) prescribing information. (dated 1998 Jun). In: Physicians' desk reference. 54th ed. Montvale NJ: Medical Economics Company Inc; 2000:655-7.
Fenta**NYL**[5]	1. 10 mcg/mL 2. 50 mcg/mL	mcg/hour	No	1. Extended Stability for Parenteral Drugs 6th Edition, 2017. Ed. Bing, CD et. al. ASHP, 4500 East-West Highway, Suite 900, Bethesda, MD 20814 2. Hospira, INC. Fentanyl Citrate injection, solution.prescribing information. Lake Forest, IL; 2019, December.
Furosemide	1. 2 mg/mL 2. 10 mg/mL	mg/hour	No, and the 10 mg/mL is administered undiluted	1. Negro S, Rendon AL, Azuara M, et.al. Compatibility and Stability of Furosemide and Dexamethasone Comined in Infusion Solutions. Arzneimittelforschung. 2006;56:714-20. 2. American Pharmaceutical Partners, Inc. Furosemide Injection, USP prescribing information. Schaumburg, IL; 2002 Apr.
Heparin[6]	100 units/mL	units/hour or units/kg/hour	Yes	1. B.Braun Medical Inc. Heparin Sodium in Dextrose Injection prescribing information. Bethlehem, PA. 2018. April

Drug	Concentration Standards	Dosing units	Commercially available	References
HYDROmorphone[5]	1. 0.2 mg/mL 2. 1 mg/mL 3. 5 mg/mL (based upon high dose requirements	mg/hour	No	1. Ensom MHH, DeCarie D, Leung K, et al. Stability of hydromorphone-ketamine solutions in glass bottles, plastic syringes, and IV bags for pediatric use. *Can J Hosp Pharm*. 2009; 62(2):112b. 2. Extended Stability for Parenteral Drugs 6th Edition, 2017. Ed. Bing, CD et. al. ASHP, 4500 East-West Highway, Suite 900, Bethesda, MD 20814 3. Extended Stability for Parenteral Drugs 6th Edition, 2017. Ed. Bing, CD et. al. ASHP, 4500 East-West Highway, Suite 900, Bethesda, MD 20814
Insulin (regular)	1 unit /mL	units/hour, DKA protocols may require units/kg/hour	No	1a. Nolan PE, Hoyer GL, LeDoux JH et al. Stability of ranitidine hydrochloride and human insulin in 0.9% sodium chloride injection. *Am J Health-Syst Pharm*. 1997. 1b. Product Information: HUMULIN(R) R subcutaneous injection, intravenous injection, insulin human subcutaneous injection, intravenous injection. Lilly USA LLC (per FDA), Indianapolis, IN, 2018. Micromedex
Isoproterenol[6]	4 mcg/mL	mcg/min or mcg/kg/min	No	1. ISUPREL (R) IV injection, isoproterenol hcl IV injection. Hospira, Inc, Lake Forest, IL, 2004.
Labetalol	5 mg/mL	mg/min	No	1. Product Information: labetalol HCl intravenous injection, labetalol HCl intravenous injection. Hospira, Inc. (per DailyMed), Lake Forest, IL, 2015.
Lidocaine	8 mg/mL	mg/min	Yes	1a. Stewart JT, Warren FW. Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm*. 1994; 51:1802–7. 1b. Product Information: Lidocaine HCl dextrose 5% intravenous injection, lidocaine HCl dextrose 5% intravenous injection. Baxter Healthcare Corporation (per FDA), Deerfield, IL, 2017.
LORazepam	1 mg/mL	mg/hour	No	1. ASHP Interactive Handbook on Injectable Drugs Accessed July 13,2020

Drug	Concentration Standards	Dosing units	Commercially available	References
Morphine[6]	1. 1 mg/mL 2. 5 mg/mL (based upon high dose requirements)	mg/hour	Yes	1. Stiles ML, Tu YH, & Allen LV Jr: Stability of morphine sulfate in portable pump reservoirs during storage and simulated administration. *Am J Hosp Pharm* 1989; 46:1404-1407. 2a. Stiles ML, Tu YH, & Allen LV Jr: Stability of morphine sulfate in portable pump reservoirs during storage and simulated administration. *Am J Hosp Pharm* 1989; 46:1404-1407. 2b. Altman L, Hopkins RJ, Ahmed S, et al: Stability of morphine sulfate in Cormed III (Kalex) intravenous bags. *Am J Hosp Pharm* 1990; 47:2040-2042.
Midazolam	1 mg/mL	mg/hour	No	1a. Karlage K, Earhart Z, Green-Boesen K, Myrdal PB. Stability of midazolam hydrochloride injection 1-mg/mL solutions in polyvinyl chloride and polyolefin bags. *Am J Health Syst Pharm*. 2011;68(16):1537-1540.[PubMed 21817086] 1b. McMullin ST, Schaiff RA, and Dietzen DJ, "Stability of Midazolam Hydrochloride in Polyvinyl Chloride Bags Under Fluorescent Light," *Am J Hosp Pharm*, 1995, 52(18), 2018-20.
Milrinone	200 mcg/mL	mcg/kg/min	Yes	1a. Wilson TD, Forde MD, Crain AVR, Dombrowski LJ, Joyce MA. Stability of milrinone in 0.45% sodium chloride, 0.9% sodium chloride, or 5% dextrose injections. *Am J Hosp Pharm*. 1986;43(9):2218-2220. 1b. Wong F, Gill MA. Stability of milrinone lactate 200 mcg/mL in 5% dextrose injection and 0.9% sodium chloride injection. *Int J Pharm Compound*. 1998; 2(2):168b
Ni**CAR**dipine	1. 0.1 mg/ml 2. 0.5 mg/ml	mg/hour	Yes - 0.1 mg/mL	1. Product Information: CARDENE(R) IV solution for IV infusion, nicardipine HCL solution for IV infusion. EKR Therapeutics, Inc, Bedminster, NJ, 2014. 2. Baaske DM, DeMay JF, Latona CA, et al. Stability of Nicardipine Hydrochloride in Intravenous Solutions. *Am J Health Syst Pharm*. 1996;53(14):1701-1705
Nitroglycerin	200 mcg/mL	mcg/min	Yes	1. Product Information: Nitroglycerin Injection. Abbott Laboratories, North Chicago, IL, October 2014

Drug	Concentration Standards	Dosing units	Commercially available	References
Nitroprusside	1. 200 mcg/mL 2. 500 mcg/mL	mcg/kg/min	No	1. Product Information: NIPRIDE RTU intravenous injection, sodium nitroprusside intravenous injection. Exela Pharma Sciences, LLC (per FDA), Lenoir, NC, 2017. 2. Product Information: NIPRIDE RTU intravenous injection, sodium nitroprusside intravenous injection. Exela Pharma Sciences, LLC (per FDA), Lenoir, NC, 2017.
Norepinephrine[4]	1. 16 mcg/mL 2. 32 mcg/mL 3. 128 mcg/mL	mcg/kg/min	No	1. Tremblay M, Lessard MR, Trepanier CA, et al: Stability of norepinephrine infusions prepared in dextrose and normal saline solutions. *Can J Anaesth* 2008; 55(3):163-167. 2. Hasegawa GR, Eder JR. Visual compatibility of dobutamine hydrochloride with other injectable drugs. *Am J Hosp Pharm* 1984;41:949-51. 3. Closset M, Hecq JD, Soumoy L, et al, "Physical stability of highly concentrated injectable drugs solutions used in intensive care units," *Ann Pharm Fr*, 2017; Volume 75: pp. 185-188. Concentration used (120 mcg.ml)
Phenylephrine	1. 80 mcg/mL 2. 400 mcg/mL	mcg/kg/min	No	1a. West-Ward Pharmaceuticals. Phenylephrine hydrochloride injection prescribing information. Eatontown, NJ; 2012 Dec 1b. Éclat Pharmaceuticals. Vazculep® (phenylephrine hydrochloride) injection prescribing information. Chesterfield, MO; 2014 2. Jansen JJ, Oldland AR, Kiser TH. Evaluation of phenylephrine stability in polyvinyl chloride bags. *Hosp Pharm*. 2014; 49:455-7.
Propofol	10 mg/mL	mcg/kg/min	Yes	1. Fresenius Kabi USA, LLC. Diprivan® (propofol) injectable emulsion prescribing information. Lake Zurich, IL; 2017 Nov.
Rocuronium[1]	10 mg/mL	mcg/kg/min	Administer undiluted	1. Hospira. Rocuronium bromide injection prescribing information. Lake Forest, IL: 2014 Feb.
Vasopressin	1. 0.2 unit/mL 2. 1 unit/mL	units/min or units/kg/min3	No	1. ASHP Interactive Handbook on Injectable Drugs Accessed July 13, 2020 2. Par Pharmaceutical Companies, Inc. Vasostrict® (vasopressin) injection prescribing information. Spring Valley, NY; 2015 Mar.
Vecuronium[1]	1 mg/mL	mcg/kg/min	No	1. Product InformationL Vecuronium bromide ntravenous injection lyophilized powder for solution. Fresenius Kabi USA, LLC (per DailyMed) Lake Zurich, IL. 2016

ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations
Use mcg for Microgram
https://www.ismp.org/tools/errorproneabbreviations.pdf

Updated: September 2021

NOTES

1 Paralytics are recommended to be administered as straight drug. This provides consistency between operating room and the ICU, and eliminates potential compounding errors.

2 This is a concentration that differs from the package insert, therefore infusion related calculations will differ from the PI

3 Consider limiting to one bag size for each recommended concentration (250 vs 500 ml). This may reduce errors and also reduce inventory needs.

4 The group intentionally made epinephrine and norepinephrine concentrations different to avoid confusion between the two agents.

5 These concentrations are for continuous infusions not delivered by a PCA device.

6 We recommend trying to standardize dosing units but understand some protocols may use "flat" dosing while others may require weight based dosing.