COMPOUNDED ORAL LIQUID 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]

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 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.

3 Joint Commission. Preventing Pediatric Medication Errors. https://www.jointcommission.org/-/media/tjc/documents/resources/patient-safety-topics/sentinel-event/sea-39-ped-med-errors-rev-final-4-14-21.pdf. (accessed March 15, 2024)

4 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)

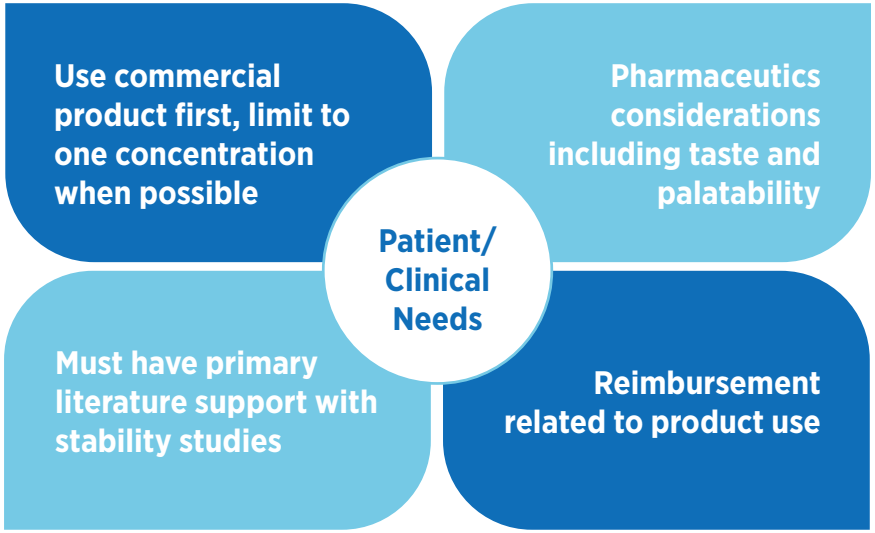
WHY STANDARDIZE

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.[5] 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,[6] 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.[7] [8] 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.[9]

HOW THE STANDARDIZED CONCENTRATIONS 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. 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 COMPOUNDED ORAL LIQUID MEDICATIONS



5 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.

6 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.

7 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.

8 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.

9 Lloyd R. Does Standardization Mean the End of Autonomy? Institute for Healthcare Improvement. https://www.ihi.org/insights/does-standardization-mean-end-autonomy. (accessed March 20, 2024)

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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 COMPOUNDED ORAL LIQUID STANDARDS

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	References
Amiodarone[1]	1. 5 mg/mL 2. 20 mg/mL for doses of 75 mg or greater	1. Nahata MC, Morosco RS, Hipple TF. Stability of amiodarone in extemporaneous oral suspensions prepared from commercially available vehicles. *J Pediatr Pharm Pract*. 1999; 4:186-9. 2. Nahata MC. Stability of amiodarone in an oral suspension stored under refrigeration and at room temperature. *Ann Pharmacother*. 1997; 31:851-2.
Atenolol	2 mg/mL	1a. Patel D, Doshi DH, Desai A. Short-term stability of atenolol in oral liquid formulations. *Int J Pharm Compound*. 1997; 1:437-9. 1b. Garner SS, Wiest DB, Reynolds ER Jr. Stability of atenolol in an extemporaneously compounded oral liquid. *Am J Hosp Pharm*. 1994; 51:508-11.
Baclofen	5 mg/mL	1. Johnson CE, Hart SM. Stability of an extemporaneously compounded baclofen oral liquid. *Am J Hosp Pharm*. 1993; 50:2353-5.
Bethanecol	5 mg/mL	1. Allen LV Jr, Erickson MA III. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline ydrochloride in extemporaneously compounded oral liquids. *Am J Health- Syst Pharm*. 1998; 55:1804-9.
Captopril	1 mg/mL	1a. Nahata MC, Morosco R, Hipple TF. Stability of captopril in liquid containing ascorbic acid or sodium ascorbate. *Am J Hosp Pharm*. 1994; 51:1707-8. 1b. Nahata MC, Morosco RS, Hipple TF. Stability of captopril in three liquid dosage forms. *Am J Hosp Pharm*. 1994; 51:95-6.
CloNIDine[2]	20 mcg/mL	1. Sauberan JB, Phuong P, Ilog, ND. Stability and osmolality of extemporeaneously prepared clonidine oral liquid for neonates. *Annals of Pharmacotherapy*. 2016;50:243-2444
Chloroquine[3]	10 mg/mL	1. Mirochnick M, Barnett E, Clarke DF. Stability of chloroquine in an extemporaneously prepared suspension stored at three temperatures. *Pediatr Infect Dis J*. 1994; 13:827-8.
Flecainide	10 mg/mL	1. Casiraghi A, Centin G, Selmin F, et.al. Critical Aspects in the Preparation of Extemporaneous Flecainide Acetate Oral Solution for Paediatrics. Pharmaceutics 2021, 13,1963.

Drug	Concentration Standards	References
Flucytosine	50 mg/mL	1. Vandenbussche H, Johnson CE, Yun J, et al. Stability of flucytosine 50 mg/mL in extemporaneous oral liquid formulation. *Am J Health-Syst Pharm*. 2002; 59:1853-5.
HydrALAZINE	4 mg/mL	1a. Nahata MC, Pai VB. Pediatric Drug Formulations. 6 th ed. Cincinnati, OH: Harvey Whitney Book; 2011. 1b. Allen LV Jr, Erickson MA III. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm*. 1998; 55:1915-20.
HydroCHLOROthiazide	5 mg/mL	1a. Allen LV, Erickson MA III. Stability of labetolol hydrochloride, metoprolol tartrate, verapamil hydrochloride and spironolactone with hydrochlorothiazide in extemperaneously compounded oral liquids. *Am J Health-Syst. Pharm*. 1996; 53:2304-2309. 1b. Binson G et al. Preparation and Physiochemical Stability of Liquid Oral Dosage Forms Free of Potentially Harmful Excipient Designed for Pediatric Patients. *Pharmaceutics* MDPI; 2019. 1c. Polonini HC et.al. Compatibility of caffeine, carvedilol, clomipramine hydrochloride, folic acid, hydrochlorothiazide, loperamide hydrochloride, methotrexate, nadolol, naltrexone hydrochloride and pentoxifylline in SyrSpend SF PH4 oral suspensions. Eur J Hosp Pharm. 2016; 23:352-358.
Hydrocortisone	2 mg/mL	1. Chong G, Decarie D, Ensom MHH. Stability of hydrocortisone in extemporaneously compounded suspension. *J Inform Pharmacother*. 2003; 13:100-10.
Hydroxyurea	100 mg/mL	1. Heeney MM, Whorton MR, Howard TA, et al. Chemical and functional analysis of hydroxyurea oral solutions. *J Pediatr Hematol Oncol*. 2004; 26:179-84.
Labetalol	40 mg/mL	1. Allen LV Jr, Erickson MA III. Stability of labetalol hydrochloride, metoprolol tartrate, verapamil hydrochloride, and spironolactone with hydrochlorothiazide in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm*. 1996; 53:2304-9.

Drug	Concentration Standards	References
Lansoprazole	3 mg/mL	1a. DiGiacinto JL, Olsen KM, Bergman KL, et al. Stability of suspension formulations of lansoprazole and omeprazole stored in amber- colored plastic oral syringes. *Ann Pharmacother*. 2000; 34:600-5. 1b. Morrison JT, Lugo RA, Thigpen JC, et al. Stability of extemporaneously prepared lansoprazole suspension at two temperatures. *J Pediatr Pharmacol Ther*. 2013; 18:122-7. 1c. Melkoumov A, Soukrati A, Elkin I, et al. Quality evaluation of extemporaneous delayed release liquid formulations of lansoprazole. *Am J Health-Syst Pharm*. 2011; 68:2069-74.
MetroNIDAZOLE	50 mg/mL	1. Allen LV, Erickson MA. *Am J Health-Syst Pharm*. 1996;53:2073- 8.
Metoprolol	10 mg/mL	1. Allen LV, Erickson MA III. Stability of labetolol hydrochloride, metoprolol tartrate, verapamil hydrochloride and spironolactone with hydrochlorothiazide in extemperaneously compounded oral liquids. *Am J Health-Syst. Pharm*. 1996; 53:2304-2309.
Morphine	400 mcg/mL	1. Sauberan JB, Rossi S, Kim, JH. Stability of dilute oral morphine solution for neonatal abstinence syndrome. *Journal of Addiction Medicine*. 2013;7:113-115.
NIFEdipine	4 mg/mL	1. Nahata MC, Pai VB. Pediatric Drug Formulations. 6th ed. Harvey Whitney Books. Cincinnati, OH, 2011.
Pyrazinamide	100 mg/mL	1. Nahata MC, Morosco RS, Peritore SP. Stapility of pyrazinamide in two suspensions. *Am J Health-Syst Pharm*. 1995;52:1558-1560.
RifAMPin	25 mg/mL	1. Allen LV Jr, Erickson MA III. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm*. 1998; 55:1804-9.

Drug	Concentration Standards	References
Sodium chloride	4 mEq/mL	1a. Using the injectable as straight drug: United States Pharmacopeia, USP 36-NF 31, General Chapter <795>, Pharmaceutical Compounding – Nonsterile Preparations. 1b. Using sodium chloride powder: United States Pharmacopeia, USP 36-NF 31, General Chapter , Pharmaceutical Compounding – Nonsterile Preparations.
Spironolactone	5 mg/mL	1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm*. 1989; 46:2040-2.
Tacrolimus	1 mg/mL	1. Elefante A, Muindi J, West K, et al. Long-term stability of a patient-convenient 1 mg/mL suspension of tacrolimus for accurate maintenance of stable therapeutic levels. *Bone Marrow Transplant*. 2006; 37:781-4.
Thioguanine	20 mg/mL	1. Aliabadi HM, Romanick M, Somayaji V, et al. Stability of compounded thioguanine oral suspensions. *Am J Health-Syst Pharm*. 2011; 68:900-8.
Topiramate[4]	20 mg/mL	1. U.S. Pharmacopeia/National Formulary [current revision]. Rockville, MD: *U.S. Pharmacopeial Convention*, Inc; April 2017.
Ursodiol[5]	60 mg/mL	1a. Johnson CE, Nesbitt J. Stability of ursodiol in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm*. 1995; 52:1798-800. 1b. Nahata MC, Pai VB. Pediatric Drug Formulations. 6th ed. Cincinnati, OH: Harvey Whitney Book; 2011.
ValACYclovir	50 mg/mL	1. Fish DN, Vidaurri VA, Deeter RG. Stability of valacyclovir hydrochloride in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm*. 1999;56:1957-1960.

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NOTES

1 Amiodarone needs to have a pH very close to 8 to assure particle consistency.
2 ISMP has recommended clonidine concentrations be displayed as mcg/mL and not mg/mL given the most common doses used. This may need to be addressed for ordering the drug and what is placed on pharmacy labels on products dispensed.
3 Chloriquine label should state the 10 mg/ml concentration reflects base chloroquine and not the chloroquine salt.
4 The topiramate concentration is copyright protected by USP and can be used for internal purposes only.
5 The formulation for the ursodiol concentration is based on the capsule dosage form and not the tablet dosage form.