Introduction

The Food and Drug Administration (FDA), through its Safe Use Initiative, awarded ASHP a three-year contract to develop and implement national standardized concentrations for intravenous (IV) and oral liquid medications. *Standardize 4 Safety* is the first national, interprofessional effort to standardize medication concentrations in order to reduce errors and improve transitions of care. ASHP is partnering with national patient safety organizations such as the Pediatric Pharmacy Association (PPAG), the Institute for Safe Medication Practices (ISMP), the Association for the Advancement of Medical Instrumentation (AAMI), and regional and local healthcare organizations to further this work. Working with partner organizations, hospitals, and pharmacist, nurse, and physician experts from across the care continuum, *Standardize 4 Safety* is creating, testing, publicizing, and supporting the adoption of these national standardized medication concentrations.

These national standards will cover:

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

This document includes the release of the first set of standards, Phase I of the IV project: adult continuous IV medications.

Purpose

The primary focus of this document is to provide evidence-based and clinical experienced guidance on optimal concentrations of IV continuous infusions for both adult ($\geq$50 kg) and pediatric (<50 kg) patients. Its additional purpose is to provide background information about the IV arm of the standardization project and about using standardization as an error-reducing strategy.

Disclaimers

- This project is supported by a contract with the FDA, Safe Use Initiative, FDA-BAA-15-00121, Section 8.5.
- This document is a working draft. Additional sections and lists will be added as the project moves forward.
- 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 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 (eMAR), 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.

Background

The effort to standardize IV concentrations started in 2008 when a multistakeholder IV summit was held in Maryland to address preventing patient harm and death from IV medication errors.[1] Three main barriers were identified at the summit:

- Lack of standardization and good process design for IV medications
- Lack of shared accountability for safety among members of different healthcare disciplines
- High-volume, high-demand environments in which safety may be sacrificed for other priorities

The participants recommended establishment of national standards for IV medications in hospitals and health systems that would include the drug name, recommended dosing range limits, upper and lower limits that should not be overridden, and standardized concentrations and dosing units. Participants also encouraged collaboration with the FDA and the pharmaceutical industry in these efforts. Despite delays due to urgent priorities such as drug shortages and compounding quality issues, interest in this effort has remained high. Stakeholders continue to believe in the value of standardization and its potential to reduce errors. For example, ASHP members have driven the creation and release of positions related to the standardization of IV drug concentrations and oral liquid concentrations.[2]

Many organizations are now targeting a goal of zero harm,[3,4] a goal that includes harm related to medication errors. Health systems have identified bundles, such as central-line blood stream infections (CLABSI) or catheter-associated urinary tract infections (CAUTI), for error prevention and harm reduction. There is evidence that implementation of integrated EHRs and use of CPOE, intelligent infusion devices, and bar-code scanning can reduce medication errors.[5,6,7,8,9] The piece of the puzzle that is missing but attainable is standardization of information fed into these electronic systems. The project overview is attached in an appendix to this document.

Statement of the Problem

Despite longtime interest from patient safety advocates, there is no national consensus for standard concentrations of IV medications (continuous, intermittent, etc). Patients are transferred between patient care areas within hospitals and between hospitals within cities and states, and across state lines. Each time a patient needs an IV medication, there is potential for error if a concentration different from the previous patient care area is used. Patients most at risk for these errors are often the most vulnerable populations: critically ill patients and extremely high-risk patients such as neonates, for who even the slightest mistake could be deadly.

Scope

Within the realm of IV solutions and smart infusion devices, there are many different aspects that have significant implications for patient safety initiatives. Each of these aspects is important. However, to maximize our impact and use our resources effectively, infusions and concentrations in this reference are limited to commonly used or high-alert drugs administered by continuous infusion for both adult and pediatric patients. The following areas of work are *excluded* from this project:

- Infusions related to extracorporeal modalities (Extracorporeal Membrane Oxygenation, Continuous Renal Replacement Therapies, etc.)
- Concentrations for nontreatment indications (i.e., heparin for line patency, etc.)
- Compounded infusions final volumes
- Diluents — selection of dextrose, saline, or a combination
- Library nomenclature and profile naming
- Chemotherapy drugs

Phases of the IV project

- Phase I — Adult (≥50kg) continuous infusions. There will be two versions of this list, 1.01 and 1.02. Version 1.01 has been finalized and includes 32 of the most commonly used or high-alert medications administered via continuous IV infusion. Chemotherapy agents will not be included in the project.
- Phase II — Pediatric (<50kg) continuous infusions. There will be two versions of this list, 1.01 and 1.02. These will be made available in 2017.
- Phase III — IV intermittent, PCA/epidural medications. This is the final phase of the IV arm of the project.

Goals

Goal 1. Form a nationwide expert faculty panel. This panel is an interprofessional panel consisting of physicians, nurses, and pharmacists. The disciplines of those involved include critical care, operating or procedural areas, emergency rooms, and medication safety. A roster of the expert panel for adult continuous infusions is attached as an appendix to this document.

Goal 2. Create the standards. The panel will determine the standard concentration formulary. Inclusion in the formulary is based on the following criteria:

- Administration is by continuous infusion or continuous plus loading/intermittent infusion only. This formulary does not apply to intermittent, perfusion, and other extracorporeal circuits. The section of the formulary pertaining to <50kg continuous infusions will be released in year 2 of the project. The section pertaining to IV intermittent, PCA/epidurals will be released in year 3 of the project.
- Each drug is limited to one or two recommended concentrations that will serve the needs of most patients in the care settings where the drug is most commonly used. The 80/20 rule, the principle that roughly 80% of the effects come from 20% of the causes, will be applicable.
- **NOTE:** Concentrations are expressed as amount of drug/mL.

Goal 3. Disseminate the standards and assess their adoption. Mass adoption of national standardized concentrations will create the possibility for a number of efficiencies or error-reduction strategies. The potential to create these conditions provides an incentive for organizations to adopt the national standardized concentration lists. Mass adoption of standardized concentrations will potentially:

- Allow for commercially manufactured products or products compounded by regulated compounding outsourcers in these concentrations, thereby increasing quality and decreasing error potential.
- Lead to decreased turnaround dispense times for life-saving medications for critically ill patients.
- Streamline ordering for prescribers through more efficient standard order sets.
- Enable better prebuilt smart pump libraries, thereby minimizing burden and associated costs for hospitals and health systems.

In addition to disseminating the standards, ASHP will encourage the formation of conditions that incentivize standardization, and will support and assess adoption of the standards.

Methods

I. Formation of expert panels

a. Created an interprofessional panel that included physicians, nurses, and pharmacists.
b. Members were chosen based on expertise in critical care, anesthesia, and ED/trauma, as well as medication safety and infusion pump knowledge
c. The American Society of Anesthesiologists (ASA), Society of Critical Care Medicine (SCCM), and American Association of Critical-Care Nurses (AACN) provided recommendations of physician and nurse representatives.
d. The current panel has 14 members (3 physicians, 3 nurses, 7 pharmacists, 1 informaticist).

II. Data Analysis

a. Data was collected from a variety of diverse sources:
    i. Standardized lists from state and regional efforts in Maine, Indiana, North Carolina, and San Diego
    ii. Information gathered from the 2008 IV Summit
    iii. Information previously gathered by the University of Utah Drug Information Service
    iv. Expert panel members' lists from their respective organizations
    v. De-identified information from 503b companies
    vi. Other offerings from large health systems nationwide
b. A draft list was released for public comment, and then revisions were conducted based on feedback collected.

III. Meetings

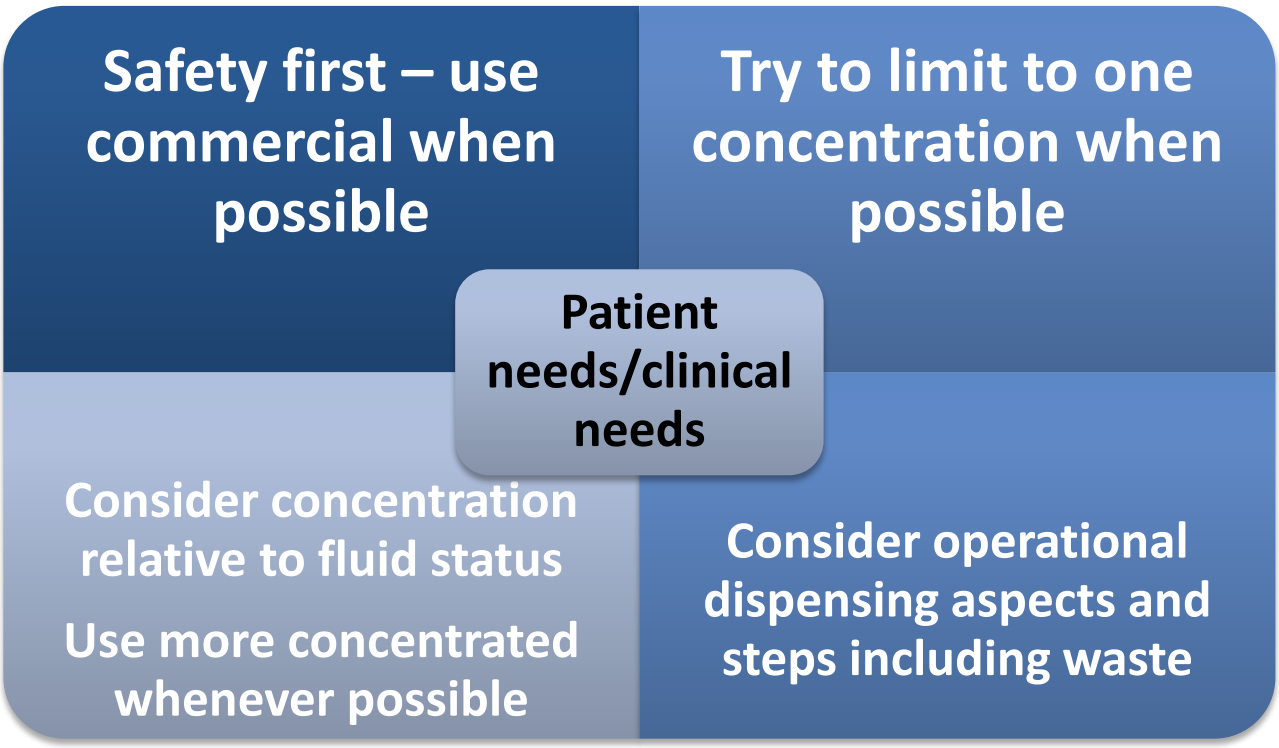
a. The expert panel convened in March 2016 to review the list and narrow the scope for version 1.01 to 32 drugs.
b. Expert panel members continue to have one to two calls per month to continue work.

IV. Guiding Principles

The panel used a set of guiding principles (illustrated using the decision matrix tool below) in order to process the large amount of data and make effective and evidence-based decisions in reaching consensus. These principles were followed in descending order of priority:

1. The patient's needs always come first.
2. Use commercially available products whenever possible. This takes advantage of manufacturers' stringent GMP requirements to ensure sterility and minimize errors.
3. Strive for one concentration, understanding that sometimes two to three concentrations may be necessary to serve extreme situations — use the 80/20 rule.
4. Consider the patient's fluid status; try to use more concentrated formulations when feasible so patients can receive more nutrition (IV or enterally).
5. Consider operational issues during compounding. Try to optimize vial sizes to decrease costs and waste in the midst of critical drug shortages.

6. Consider average doses of medications used, and avoid compounded concentrations that may exceed a 24-hour supply of the drug.



Decision Matrix Tool

V. Quality control

a. The finalized list has been reviewed by expert panel members, internal ASHP staff, and ISMP for accuracy of drug name, concentrations, and dosing units.
b. ASHP used the FDA and ISMP recommendations for tallman lettering.
c. ASHP validated with the FDA that it is permissible to recommend a concentration other than that stated in the PI, given the inclusion of a disclaimer statement and the existence of evidence-based published literature for the concentration recommended.

References

1. Proceedings of a summit on preventing patient harm and death from i.v. medication errors. July 14-15, 2008, Rockville, Maryland. Am J Health-Syst Pharm. 2008; 65:2367-79.

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

3. Chassin MR, Loeb JM. The ongoing quality improvement journey: next stop, high reliability. Health Affairs 2011; 30:559-68.

4. Chassin MR, Loeb JM. High reliability health care: getting from there to here. The Milbank Quarterly 2013; 91: 459-90.

5. Kelly WN, Rucker TD. Compelling features of a safe medication-use system. Am J Health Syst Pharm. 2006; 63(15):1461-83.

6. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Archives of Internal Medicine. 2003; 163:1409-16.

7. Cutler DM, Feldman NE, Horwitz JR. U.S. adoption of computerized physician order entry systems. Health Affairs. 2005; 24(6):1654-63.

8. Marini SD, Hasman A. Impact of BCMA on medication errors and patient safety: a summary. Studies in Health Technology and Informatics 2009; 146:439-44.

9. 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:e21-5.

Drug	First concentration	Second concentration	Third conc	Dosing units	Commercially available	Comments
Alteplase	1 mg/mL			mg/hour	Yes, comes in a kit with diluent	This concentration is for treatment doses only and does not apply to interventional radiology needs and/or catheter treatments. Available in drug kits of 50 mg or 100 mg vials with diluent included
Amiodarone	1.5 mg/mL	3.6 mg/mL		mg/min	Yes	Two concentrations needed, 1.5 mg/mL for peripheral, 3.6 mg/mL for central. Some institutions were using 1.8 mg/mL but still seeing phlebitis.
Argatroban	1 mg/mL			mcg/kg/min	Yes	
Bumetanide	0.25 mg/mL			mg/hour	Administer undiluted	
Cisatracurium	2 mg/mL[1, 2]			mcg/kg/min	Administer undiluted	The package insert (PI) has infusion information using 0.4 mg/mL
Dexmedetomidine	4 mcg/mL			mcg/kg/hour	Yes	Only concentration recommended in package insert also commercially available product
Dil**TIAZ**em	1 mg/mL			mg/hour	No	Hospira has advantage 100 mg/100 mL (may be similar products)- using the manufacturer vial of 125mg the admixture would be 125 mg in 125 mL unless not accounting for any overfill of the bag
DOBUTamine	4000 mcg/mL			mcg/kg/min	Yes	Premix bag -considerations may be needed for areas performing diagnostic tests - in addition to what is needed in home care setting. No evidence to dispute 4000 mcg/mL cannot be given via peripheral route
DOPamine	1600 mcg/mL	3200 mcg/mL		mcg/kg/min	Yes	Premix bags, consider limiting to one bag size of each (250 vs. 500 mL, could reduce inventory needs and errors)
EPINEPHrine	20 mcg/mL	40 mcg/mL		mcg/kg/min	No	vial size 1 mg/mL or 30 mg/30 mL. The group intentionally made these concentrations different from those for norepinephrine in order to avoid confusion between the two agents.
Esmolol	10 mg/mL	20 mg/mL		mcg/kg/min	Yes	10 mg/mL for peripheral, 20 mg/mL for central. Most institutions use the 10 mg/mL premix but dosing ranges indicate the 20 mg/mL is more appropriate based upon fluid volumes.
Fenta**NYL**[4]	10 mcg/mL	50 mcg/mL		mcg/hour	No	Ease of prep, can make 2500 mcg (50 mL) in 250mL to make 10 mcg/mL (need to remove volume of drug and overfill) or use straight drug of 50 mcg/mL
Furosemide	2 mg/mL	10 mg/mL		mg/hour	No, and the 10 mg/mL is administered undiluted	This is highly dependent upon using low dose continuous infusions (doses less than 10 mg/hour) or using high doses (20 mg/hour or more)

Drug	First concentration	Second concentration	Third conc	Dosing units	Commercially available	Comments
Heparin	100 units/mL			units/hour or units/kg/hour[3]	Yes	This comes in a commercially available bag, also recommend stocking one bag volume. This concentration is for treatment, systemic anticoagulation and is not for line patency, arterial-lines, etc. Hospitals should try to standardize the dosing units, however we recognize that weight based and flat dose is used in practice given indication. Please just try to be clear for nursing on the eMAR and in the smart pump programming to prevent errors
HYDROmorphone[4]	0.2 mg/mL	1 mg/mL	5 mg/mL (based upon high dose requirements)	mg/hour	No	This is for hydromorphone infusions NOT via PCA pump infused on other continuous devices. Only consider the 5 mg/mL for patients with high dose needs. PCA concentrations will be in phase III of the project
Insulin (regular)	1 unit /mL			units/hour, DKA protocols may require units/kg/hour	No	compounded - 100 units in 100 mL NS or 250 units in 250 mL. We do not endorse using 0.1 units/mL in OB protocols as this is a signficant error potential when pharmacies are compounding and the 1 unit/mL can be easily titrated
Isoproterenol	4 mcg/mL			mcg/min or mcg/kg/min[3]	No	We recommend standardizing dosing units but understand current protocols may use flat dosing or weight based dosing units. A second concentration may be needed by heart transplant centers
Labetalol	5 mg/mL			mg/min	No	Typically the normal dosing ranges warrant the higher 5 mg/mL concentration
Lidocaine	8 mg/mL			mg/min	Yes	Based upon typical doses the 4 mg/mL concentration doesn't seem to be clinically needed. However this could have an operational impact on bags in ACLS crash carts
LORazepam	1 mg/mL			mg/hour	No	100 mg in 100 mL or 50 mg in 50 mL -- very consistent concentration amongst everyone. If institutions use 2 mg/mL (straight drug), this is very viscous
Morphine[4]	1 mg/mL	5mg/ml based upon high dose requirements		mg/hour	Yes	The 1 mg/mL is commercially available. These are NOT concentrations for PCA pump and for other continuous infusion pumps used in the ICU
Midazolam	1 mg/mL			mg/hour	No	consistent across the board, 10 mL of 5 mg/mL vials so no waste (50 mg in 50 mL or 100 mg in 100 mL)
Milrinone	200 mcg/mL			mcg/kg/min	Yes	commercial - most using 200 mcg/mL. Ambulatory heart failure patients -- hospitals may need to add another concentration for outpatient needs
Ni**CAR**dipine	0.1 mg/ml	0.5 mg/mL		mg/hour	Yes - 0.1 mg/mL	does come as 0.1 mg/mL commercially available. Chose 2 concentrations the 0.1 mg/mL can be use peripherally, the 0.5 mg/mL only CENTRALLY and fluid restricted patients

Drug	First concentration	Second concentration	Third conc	Dosing units	Commercially available	Comments
Nitroglycerin	200 mcg/mL			mcg/min	Yes	the 400 mcg/mL has been on and off the shortage list
Nitroprusside	200 mcg/mL	500 mcg/mL		mcg/kg/min	No	Vials are 50 mg, 1 vial 50 mg in 250 mL = 200 mcg/mL, 1 vial 50 mg in 100 mL = 500 mcg/mL
Norepinephrine	16 mcg/mL	32 mcg/mL	128 mcg/mL	mcg/kg/min	No	4 mg in 250 mL = 16 mcg/mL, 8 mg in 250 mL = 32 mcg/mL, 32 mg in 250 mL = 128 mcg/mL. The higher concentration is needed for hospitals with large trauma centers and/or severe fluid restriction in critically ill with high dosing needs
Phenylephrine	80 mcg/mL	400 mcg/mL		mcg/kg/min	No	10 mg, 50 mg, 100 mg vials , 20 mg in 250 mL (80 mcg/mL), 100 mg in 250 mL (400 mcg/mL). The higher concentration is for central line use only and is needed for hospitals with large trauma centers and/or severe fluid restriction in critically ill with high dosing needs
Propofol	10 mg/mL			mcg/kg/min	Yes	
Rocuronium	10 mg/mL[1]			mcg/kg/min	Administer undiluted	
Vasopressin	0.2 unit/mL	1 unit/mL		units/min or units/kg/min[3]	No	Concentration recommended now by manufacturer with new product - these concentrations are for cardiac/vasopressor indications. We recommend standardizing dosing units but understand current protocols may use flat dosing or weight based dosing units. Phase 2 will be Diabetes Insipidus concentrations
Vecuronium	1 mg/mL[1]			mcg/kg/min	No	10 mg vials, typically dilute with NS

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

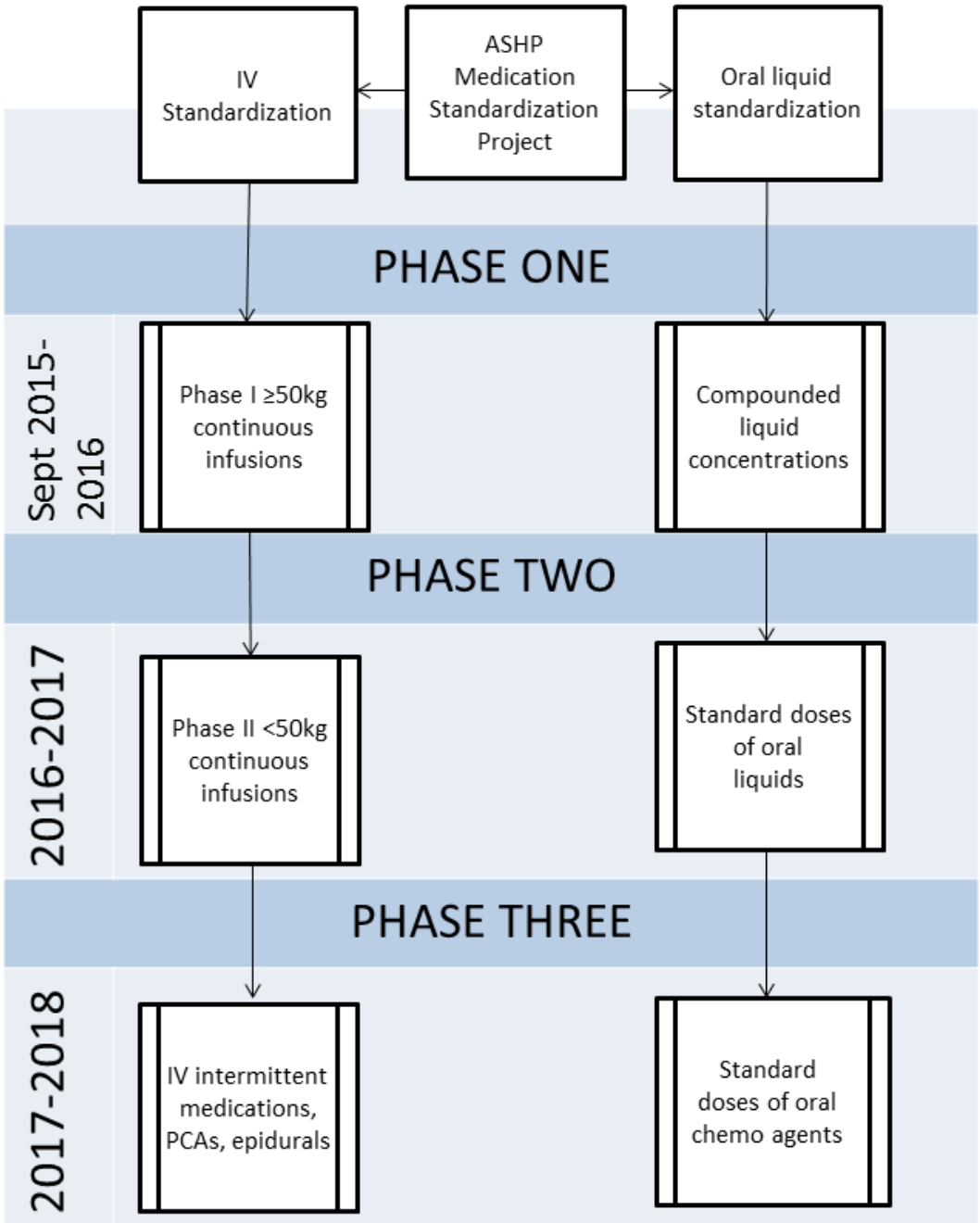
1. Paralytics are recommended to be administered as straight drug. The reason for this is consistency between the operating room and the intensive care unit. In addition further compounding in the pharmacy is a potential source of additional errors.

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

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

4. These concentrations are for continuous infusions not delivered by a PCA device. PCA concentrations will be determined in stage III of the project

Appendix A: *Standardize 4 Safety* Project Overview



Appendix B: IV Continuous Infusion ≥50kg Expert Panel

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