Calcium and phosphate compatibility: Revisited again

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The subject of the compatibility between calcium and phosphates was revisited in an April 1994 FDA safety alert, 6–16 years after the four seminal research articles appeared in 1978, 1980, 1982, and 1988. In the 1980s there were two case reports of nonfatal adverse events involving calcium phosphate precipitation in total parenteral nutrient (TPN) admixtures. A review of the main determinants of parenteral drug and admixture compatibility and stability also appeared during that decade. Soon after the April 1994 safety alert, several publications on calcium phosphate precipitation in TPN formulations appeared. Thus, this article is yet another revisit of calcium and phosphate compatibility with i.v. formulations.

This article discusses the chemistry and practical compatibility or solubility factors relevant to the safe administration of combination therapy with calcium gluconate and potassium or sodium phosphate injections. Patient case reports that led to adverse events and pharmaceutical and clinical factors important to calcium phosphate solubility are also presented.

pH and pK<sub>a</sub> equilibria relevant to calcium and phosphate compatibility. The keys to understanding the chemical reactions and relative risks for calcium phosphate precipitation are as follows:

- The clinically relevant dissociation equilibria for which the pK<sub>a</sub> of phosphoric acid is 7.2 (i.e., the pH at which the concentrations or, thermodynamically, the ionic activities of HPO<sub>4</sub><sup>2-</sup> and H<sub>2</sub>PO<sub>4</sub><sup>-</sup> are equal) (Table 1):

  \[ \text{OH}^{-} + \text{H}_2\text{PO}_4^{-} \leftrightarrow \text{HPO}_4^{2-} + \text{H}_2\text{O}; \text{shifts to right when pH increases} \] (1)

  \[ \text{H}_2\text{O} + \text{H}_2\text{PO}_4^{-} \leftrightarrow \text{HPO}_4^{2-} + \text{H}_3\text{O}^{+}; \text{shifts to left when pH decreases} \] (2)

- The Henderson–Hasselbach equations:

  \[ \text{pH} = \text{pK}_a + \log \left( \frac{[A^{-}]}{[HA]} \right) \] (3)

  \[ \text{pH} = \text{pK}_a + \log \left( \frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^{-}]} \right); \text{percent HPO}_4^{2-} = 100\left(1 + \text{antilog} \left[ \text{pK}_a - \text{pH} \right] \right) = 100/\left(1 + \text{antilog} \left[ \text{pK}_a - \text{pH} \right] \right) \] (4)

- The compatibility curves for calcium gluconate versus phosphate concentrations in clinical mixtures.

- The influence of other drugs and nutrients.

The application of knowledge about calcium and phosphate compatibility in i.v. therapy has been facilitated by four hallmark articles, several editions of the Handbook on Injectable Drugs since 1983, and Trissel’s Calcium and Phosphate Compatibility in Parenteral Nutrition. Despite the availability of these literature sources, calcium and phosphate compatibility continues to be a clinical enigma.

Physicochemical factors. Calcium and phosphate solubility chemistry. The aqueous chemistry and solubility of the two phosphate anions and their calcium salts that are important to the safety of i.v. therapy are summarized in Table 1. The main facts are as follows: The lower the solution pH is below 7.2, which is the critical pK<sub>a</sub> of phosphoric acid in practice, the greater is the majority percentage of the desired H<sub>2</sub>PO<sub>4</sub><sup>-</sup> anion (dihydrogen or monobasic phosphate). HPO<sub>4</sub><sup>2-</sup>, with two dissociable protons, is an acid relative to H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, and HPO<sub>4</sub><sup>2-</sup> (i.e., monohydrogen or dibasic phosphate) is a base or weaker acid relative to H<sub>2</sub>PO<sub>4</sub><sup>-</sup>. Ca[H<sub>2</sub>PO<sub>4</sub>]<sub>2</sub> (calcium dihydrogen phosphate) is 60 times more soluble than CaHPO<sub>4</sub> (calcium monohydro-

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gen phosphate), because CaHPO$_4$ is less dissociated.\textsuperscript{19,20} Note that, typical of most divergent cation--divalent anion salts, CaHPO$_4$ is minimally solvated into its constituent ions. Consequently, most of the Ca$^{2+}$ and HPO$_{4}^{2-}$ ions cannot be solvated by dipolar water molecules via ion--dipole intermolecular forces, resulting in 0.3-mg/mL solubility in water. Ion--dipole forces generally result in greater solubility in water than do other types of solute--water intermolecular forces.\textsuperscript{19,20} The contrasting high solubility of the diivalent cation--divalent anion, magnesium sulfate, at more than 500 mg/mL, results from dipole--dipole forces between water and the mostly nondissociated MgSO$_4$ ion pairs, which are dipoles. The efficient water solubility of some nonionic organic compounds (e.g., sugars) results from accepting and donating multiple intermolecular hydrogen bonds with water (i.e., one hydrogen bond for at least every four carbon atoms).\textsuperscript{20}

The percentages of H$_2$PO$_4^-$ and HPO$_{4}^{2-}$ decrease and increase, respectively, by 1.6% to 5.7% for each 0.1 pH unit increase over the pH range of 6.0–7.6.\textsuperscript{14} Because 1 meq of HPO$_{4}^{2-}$ corresponds to 2 meq of H$_2$PO$_4^-$, phosphate concentration should be expressed in millimoles per liter, not in milliequivalents per liter. In the article by Schuetz and King,\textsuperscript{3} phosphates were reported in milliequivalents per liter, not in millimoles per liter but without specific concentrations of H$_2$PO$_4^-$ and HPO$_{4}^{2-}$. The appendix shows the calculation for milliequivalents of potassium and for millimoles of phosphates per milliliter in commercial Potassium Phosphates Injection, USP, and for millimoles of calcium per milliliter in commercial 10% Calcium Gluconate Injection, USP.

Before the transition to the Pharm.D. degree began achieving national momentum in the 1970s, most U.S. pharmacy schools required courses in qualitative and quantitative chemical analysis and inorganic pharmaceutical chemistry. Those courses were particularly pertinent to the solubility of calcium salts, as illustrated by the following excerpt from a monograph on CaHPO$_4$ in a standard pharmacy textbook from 1967: “Because this salt is almost insoluble in water, its chemical reactions are few and relatively unimportant. It is soluble in diluted hydrochloric acid.”\textsuperscript{15} That CaHPO$_4$ is more soluble at increasingly acidic pH represents the leftward shift in equation 2, and the “unimportance” of CaHPO$_4$ reactions stated in the 1967 source ended in 1968 with the report that launched TPN,\textsuperscript{21} which made reactions between calcium and phosphates in i.v. formulations a matter of life and death.

**Calcium and phosphate solubility for i.v. therapy.** It is unlikely that any patient-specific i.v. admixture containing calcium and phosphates will exactly duplicate the compatibility results of published studies. Three common variables are (1) practitioner and device volume-measurement accuracy and precision, (2) content and pH ranges from *The United States Pharmacopeia* and *The National Formulary* (USP) for calcium gluconate injection (i.e., 95–105% of labeled content and pH 6.0–8.2) and for potassium and sodium phosphate injections (i.e., 95–105% of labeled content),\textsuperscript{22} and (3) other drugs and nutrients that may be included in i.v. admixtures (i.e., the variable composition of TPN formulations, which are often patient specific). Even small differences in the USP-allowed percent content ranges of calcium gluconate and potassium or sodium phosphate injections may contribute to the precipitation or nonprecipitation of CaHPO$_4$ in clinical practice.

The main factors that are important to ensuring total solubility or compatibility of calcium and phosphates in TPN and other i.v. therapy are as follows:\textsuperscript{1,18}:

- The mixture should be agitated to achieve homogeneity after each ingredient is added.
- Potassium or sodium phosphate injection should be added early, and calcium gluconate injection should be added last or nearly last to the last dilute phosphate concentration possible.\textsuperscript{1,2,17,18}
- A 0.2-µm air-eliminating sterile inline filter should be used for non-fat-emulsion-containing i.v. admixtures, and a 1.2-µm filter should be used for fat-emulsion-containing i.v. admixtures.\textsuperscript{1,3,10,13,14,17,18}

\begin{table}
\begin{center}
\begin{tabular}{|c|c|c|}
\hline
Ion or Salt\textsuperscript{a} & Names & Solubility (mg/mL)\textsuperscript{b,c,10} \\
\hline
H$_2$PO$_4^-$ & Monobasic\textsuperscript{c} phosphate, dihydrogen phosphate & NA\textsuperscript{c} \\
HPO$_{4}^{2-}$ & Dibasic\textsuperscript{d} phosphate, monohydrogen phosphate & NA \\
Ca[H$_2$PO$_4$]$_2$ & Monobasic calcium phosphate, calcium dihydrogen phosphate & 18 \\
CaHPO$_4$ & Dibasic calcium phosphate, calcium monohydrogen phosphate & 0.3 \\
\hline
\end{tabular}
\end{center}
\end{table}
• Calcium chloride injection should never be the calcium source in i.v. therapy that contains phosphate injections, because calcium chloride dissociates more extensively than calcium gluconate, resulting in more Ca\(^{2+}\) available to react with HPO\(_4^{2-}\), thus increasing the likelihood of CaHPO\(_4\) precipitation.\(^4,5\)

• The intersection of final calculated calcium and phosphate concentrations in clinical i.v. admixtures must be below the typical solubility curve (Figure 1).\(^4,5,7,18\)

• A single sum or product of calcium and phosphate concentrations must not be used as the sole criterion for judging compatibility, because products of calcium concentration (in milliequivalents per liter) and phosphate concentration (in millimoles per liter) vary inconsistently as calcium concentration decreases and phosphate concentration increases.\(^4,5\)

• The calculated concentrations of calcium and phosphates in TPN formulations must include all sources (e.g., amino acids injection) and not just the obvious calcium gluconate and potassium or sodium phosphate injections.

• The lower the final pH, the greater the percentage of H\(_2\)PO\(_4\)\(^-\) at which H\(_2\)PO\(_4\)\(^-\) forms more soluble calcium dihydrogen phosphate salt with Ca\(^{2+}\). Higher final concentrations of dextrose and the age-essential amino acid cysteine hydrochloride and lower final i.v. fat-emulsion concentrations favor lower admixture pH.

• The higher the final amino acid concentration, the less likely CaHPO\(_4\) is to precipitate. Some amino acids sequester Ca\(^{2+}\) (i.e., form stable soluble complexes). While most pharmacists are aware that disodium ethylenediaminetetraacetic acid (EDTA) sequesters divalent ions, including Ca\(^{2+}\), fewer of them identify EDTA as an amino acid.\(^14\)

• The rates of crystalline growth and precipitation of CaHPO\(_4\) in clinical admixtures may be variable and low in supersaturated mixtures. For example, in one study of a simulated TPN admixture, the measured calcium concentration declined exponentially from 22 to 7 meq/L over 14 days in 0.2-μm membrane filtrates of the original admixture.\(^14\) In another study of a simulated TPN admixture, an increase in CaHPO\(_4\) particles larger than 5 μm was measured over 48 hours by using light obscuration, and the precipitates were confirmed as such by petrography and infrared spectroscopy.\(^23\)

Demonstration samples of calcium gluconate and potassium phosphate injections. Table 2 illustrates the beneficial effects of the acidic pH of dextrose injection and of calcium sequestration by amino acids on the compatibility of i.v. calcium and phosphates. The approximate calcium and phosphate concentrations of 28 meq/L and 24 mmol/L, respectively, were chosen to intersect well above recommended compatibility curves (Figure 1), so that visible precipitation would occur quickly and convincingly in samples with little or no content of dextrose and amino acids.\(^18\) After thorough mixing, the ingredients were added in this order: potassium phosphates, 50% dextrose injection, sterile water for injection (nonbacteriostatic), amino acids, and calcium gluconate. The sample tubes were stored at 22–24 °C and each day were exposed to ceiling fluorescent illumination for 10 hours and to darkness for 12 hours.

The typical results for the samples listed in Table 2 are presented in Table 3. Adding a few drops of 1.9% (0.05 M) disodium EDTA to sample A or D illustrates calcium sequestration by amino acids when the precipitated CaHPO\(_4\) dissolves, and adding a few drops of 1 N hydrochloric acid to sample A or D illustrates the left-shifted equilibrium in equation 2, which favors calcium and phosphate compatibility. The change from colorless to pale yellow to yellow-amber in samples F, G, and H over 14 days.
Correlation coefficient (r) is the measure of the strength of the linear relationship between two variables. In this case, the regression of the natural logarithm of calcium concentration versus the natural logarithm of phosphate concentration yielded better correlation (r = -0.99) than the regression of the natural logarithm of calcium concentration versus phosphate concentration. Products of calcium concentration (in milliequivalents per liter) with phosphates increase from 5 to 8 mmol/L and a slope slightly below horizontal as calcium declines from 14 to 5 meq/L and phosphates increase from 8 to 23 mmol/L. For all such curves, concentration pairs beneath the curves were judged to reflect visual compatibility.

To determine the best-fit curve according to the correlation coefficient between the Figure 1 variables of calcium and phosphate concentrations, variations in the mathematical function of the concentrations were applied. The regression of the natural logarithm of calcium concentration versus the natural logarithm of phosphate concentration yielded better correlation (r = -0.99) than the regression of the natural logarithm of calcium concentration versus phosphate concentration. Products of calcium concentration (in milliequivalents per liter) with phosphates increase from 5 to 8 mmol/L and a slope slightly below horizontal as calcium declines from 14 to 5 meq/L and phosphates increase from 8 to 23 mmol/L. For all such curves, concentration pairs beneath the curves were judged to reflect visual compatibility.

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Calcium and phosphates

Commentary Calcium and phosphates

Phosphate concentration (in millimoles per liter) vary inconsistently from 130 to 170\(^4\) and from 100 to 190\(^5\) as calcium concentration decreases and phosphate concentration increases. This is why a single product should not be used as a sole criterion for judging compatibility.

Case reports. The calcium and phosphate concentrations that resulted in patient harm or death are reviewed below (Figure 3).

**Report by Robinson and Wright.**\(^7\) A right subclavian catheter became occluded after 64 days of continuous TPN therapy. The TPN admixture consisted of 500 mL of 8.5% amino acids injection and 500 mL of 50% dextrose injection in a 1000-mL formula that also contained calcium gluconate 10 meq/L and phosphate 80 mmol/L (evenly divided between the sodium and potassium salts). This phosphate concentration greatly exceeds the right-hand limit of 25 mmol/L on the phosphate axis in Figure 3. The patient survived, probably because a 0.22-\(\mu\)m inline filter was used.

**Report by Knowles et al.**\(^8\) A patient who had been receiving home TPN therapy for five years developed diffuse granulomatous interstitial pneumonitis due to exposure to precipitated \(\text{CaHPO}_4\). The TPN formulation contained 4.25% amino acids injection and 5% dextrose injection; this is a low-osmolality formulation that would be expected to be more susceptible to calcium and phosphate precipitation than, for example, the dextrose concentrations described by Henry et al.,\(^4\) Eggert et al.,\(^5\) and Fausel et al.\(^14\)

**Report by Hill et al.**\(^12\) This report, which prompted the FDA safety alert,\(^1,2\) involved four patients who had been receiving a low-osmolality TPN admixture via a peripheral vein during hospitalization at Tripler Army Medical Center in Honolulu and who developed sudden and un-

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**Table 3.**
Appearance of Samples of Calcium Gluconate and Potassium Phosphates Injections, USP, after Standing at 22–24 °C

<table>
<thead>
<tr>
<th>Sample</th>
<th>Visual Appearance at Interval Indicated(^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>A</td>
<td>3(^c)</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>1(^c)</td>
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<tr>
<td>E</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>0</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\) = no precipitate or color change, \(^{1}\) = faint turbidity from \(\text{CaHPO}_4\) precipitate, \(^{3}\) = intense turbidity from \(\text{CaHPO}_4\) precipitate, \(^{Y}\) = pale yellow, \(^{YA}_1\) = pale yellow-amber, \(^{YA}_2\) = darker yellow-amber than \(^{YA}_1\), \(^{YA}_3\) = darker yellow-amber than \(^{YA}_2\).

\(^{b}\)Sample tubes were gently agitated at each observation time to swirl any possible scant crystalline precipitate from the bottoms. White or black fungi and mold may appear as fluffy masses after several days in dextrose-containing samples, but those are easily distinguished from precipitated \(\text{CaHPO}_4\).

\(^{c}\)Precipitation occurred instantly upon the addition of calcium gluconate injection.

\(^{d}\)Clear supernatant over approximately 0.75 in-thick sediment of gelatinous-appearing precipitate.

**Figure 2.** Calcium gluconate and potassium phosphate injection samples A–H (see Tables 2 and 3) photographed at 14 days.
explained respiratory distress, which was fatal in two cases. Postmortem examination of lung tissue identified CaHPO₄ crystals in the pulmonary microvasculature. Table 4 compares the institution’s peripheral-vein and central-vein TPN formulations and illustrates most of the important calcium and phosphate compatibility factors. The deaths were attributed to an unfavorable mixing sequence, lack of inline filtration, and a short time from compounding to administration. The calcium and phosphate concentrations did not exceed the solubility limit in the final TPN admixture volume, but CaHPO₄ precipitated when calcium gluconate was added before 70% dextrose injection to only 46% of the final volume of the TPN admixture. There was not adequate time between the completion of compounding and the start of infusion for the precipitated CaHPO₄ to dissolve, nor was the formulation agitated sufficiently.

Report by Shay et al. This retrospective cohort study reviewed all hospitalized patients who received a low-osmolality and low-osmolarity formulation (peripheral-vein parenteral nutrient [PN] formulation) containing calcium and phosphate over a 16-month period. The definition for possible calcium phosphate precipitation and harm was met if “while receiving [peripheral-vein] PN during the study period, [the patient] developed unexplained chest pain, dyspnea, or cardiopulmonary arrest of noncardiac etiology or had new, unexplained bilateral interstitial infiltrates noted on chest radiograph.” Of the 50 patients who received the therapy, 5 met this definition, and 4 of them died.

Report by author. One of the authors (D.W.N.) served as a consultant in a lawsuit involving a baby’s death (after 2001) caused by precipitation of CaHPO₄ during an i.v. dextrose infusion. The confidential information provided indicated that (1) relevant literature sources were either misinterpreted or not reviewed, (2) the curve for calcium concentration versus phosphate concentration was interpreted as a downward-sloping straight line, (3) a compatibility chart for amounts of calcium gluconate and potassium phosphate injected was based on a final volume of x mL, but the actual volume compounded was 0.5x mL, resulting in twice the assumed concentrations of calcium and phosphates, and (4) an inline filter was not used. One physician who attempted to rescue the baby stated “Ten to 15 minutes into resuscitation, the lower 1–2 cm of the baby’s i.v. fluid bag, as well as the i.v. tubing, showed precipitation.”
Table 4.
Calcium and Phosphate Compatibility Factors in Central- and Peripheral-Vein Parenteral Nutrient Formulations at Tripler Army Medical Center

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Central-Vein Formulation</th>
<th>Peripheral-Vein Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose</td>
<td>24%</td>
<td>7%c</td>
</tr>
<tr>
<td>Freamine III with electrolytes</td>
<td>41 g</td>
<td>33 gf</td>
</tr>
<tr>
<td>Fat from i.v. emulsion</td>
<td>28 g</td>
<td>39 gf</td>
</tr>
<tr>
<td>Phosphorusa</td>
<td>14 mmol/L</td>
<td>15 mmol/L</td>
</tr>
<tr>
<td>Calciumb</td>
<td>5 meq/L</td>
<td>10 meq/L</td>
</tr>
</tbody>
</table>

*aFrom confidential documents provided to author (D.W.N.) as a consultant for a lawsuit in 1997.
*bA lower final dextrose concentration favors a higher final mixture pH, which favors a higher percentage of phosphate as HPO4<sup>2-</sup>, which favors greater formation of the least-soluble CaHPO<sub>4</sub> salt.
*cA lesser amino acids concentration reduces Ca<sup>2+</sup> sequestration, which increases the free Ca<sup>2+</sup> concentration available to react with phosphates.
*dA higher fat content favors a higher final mixture pH, from the alkaline pH of fat emulsion, which favors a higher percentage of phosphate as HPO4<sup>2-</sup>, which favors greater formation of the least-soluble CaHPO<sub>4</sub> salt.
*eFrom potassium phosphate injection.
*fA higher final phosphate concentration favors greater CaHPO<sub>4</sub> formation, which increases precipitation potential.
*gFrom calcium gluconate injection.
*hA higher final calcium concentration favors greater CaHPO<sub>4</sub> formation, which increases precipitation potential.

Preventing future harm. All institutions must establish calcium and phosphate mixing guidelines that are supported by peer-reviewed literature and the manufacturers’ product information. The compatibility guidelines should be based on actual clinical conditions and be reviewed and approved by the pharmacy and therapeutics committee. Low-osmolality and low-osmolarity formulations, such as PN admixtures administered through a peripheral vein, are notorious for calcium and phosphate incompatibility; thus, they should be avoided when possible. A recent investigation of such compatibility for peripheral-vein PN admixtures (≤3% amino acids and ≤5% dextrose) showed that the upper limit of compatibility was calcium gluconate 5 meq/L and sodium phosphate 15 mmol/L, or approximately half the parental equivalent of the recommended daily allowance of these minerals.[23]

In the early TPN studies used to construct the curve in Figure 1,4,5 a limited range of macronutrient concentrations was employed, and only visual identification of precipitation, which can be highly variable, was performed. Recent studies employing particle detection and size measurement by light obscuration provide objective evidence of subvisible microprecipitation,[23] which can be clinically dangerous.

Careful interpretation of the calcium and phosphate compatibility literature is necessary before application to clinical practice. For example, Wong et al.[27] recently suggested that calcium and phosphate concentrations in TPN admixtures for neonates could be doubled to meet fetal accretion rates by using a formulation containing only monobasic potassium phosphate, KH<sub>2</sub>PO<sub>4</sub>. This claim was based on the correct premise that the divalent phosphate anion, HPO<sub>4</sub><sup>2-;</sup> is the culprit in calcium phosphate precipitation in TPN formulations. However, it did not emphasize that increasing pH (e.g., pH in TPN formulations that is much higher than pH in the KH<sub>2</sub>PO<sub>4</sub> injection product) will cause the monobasic anion, H<sub>2</sub>PO<sub>4</sub><sup>-;</sup>, to convert to the dibasic anion, HPO<sub>4</sub><sup>2-;</sup>, as depicted in equation 1. In the study by Wong et al., samples were evaluated on three occasions between 0 and 27 hours after admixture preparation. Only 1 of 45 sample measurements exceeded pH 6 (i.e., 6.06) whereas most of the TPN admixtures studied by Henry et al.,[4] Eggert et al.,[5] and Fausel et al.[24] had a pH of 6.3. Wong et al.[27] would have identified CaHPO<sub>4</sub> precipitation in more samples if the pH had been higher.

Conclusion. Understanding the chemical and practical compatibility of calcium gluconate and potassium or sodium phosphate injections is critical to ensuring the safe i.v. administration of these supplements and preventing patient harm.

References


**Commentary** Calcium and phosphates

<table>
<thead>
<tr>
<th>Appendix—Calculation of calcium concentration in Calcium Gluconate Injection, USP, and phosphorus and potassium concentrations in Potassium Phosphates Injection, USP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium Gluconate Injection, USP</strong></td>
</tr>
<tr>
<td>1. Selected information from The United States Pharmacopeia and the National Formulary (USP) contains 95–105% of labeled strength of calcium gluconate. A small amount of calcium content from the gluconate salt may be replaced by calcium saccharate or other calcium salts for stabilization.</td>
</tr>
<tr>
<td>2. Typical commercial product label information: strength, 10%; calcium 0.465 meq/mL; content, calcium gluconate monohydrate 98 mg/mL and calcium saccharate tetrahydrate 4.6 mg/mL.</td>
</tr>
<tr>
<td>3. Chemical formulas and weights: calcium gluconate monohydrate, Ca(C6H11O7)2, 224 mg/mL; anhydrous monobasic potassium phosphate, KH2PO4, 136.09 g; anhydrous dibasic potassium phosphates, K2HPO4, 174.18 g.</td>
</tr>
<tr>
<td>4. Calcium gluconate monohydrate calculation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>98 mg/mL × g/mol × 2 eq/mol × 1000 meq/L = 0.437 meq/mL</td>
</tr>
<tr>
<td>5. Calcium saccharate tetrahydrate calculation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4.6 mg/mL × g/mol × 2 eq/mol × 1000 meq/L = 0.029 meq/mL</td>
</tr>
<tr>
<td>6. Sum of answers for steps 4 and 5 is 0.466 meq/mL.</td>
</tr>
<tr>
<td>7. Calcium equivalencies: 1 mmol = 2 meq (because of 2+ calcium ion valence), 1 meq = 20.04 mg.</td>
</tr>
<tr>
<td>8. Sum of answers for steps 4 and 5 is 0.466 meq/mL.</td>
</tr>
</tbody>
</table>

**Potassium Phosphates Injection, USP**

1. Selected USP monograph information: Contains 95–105% of labeled strengths of monobasic and dibasic potassium phosphates.

2. Typical commercial product label information: phosphorus, 3 mmol/mL; potassium, 4.4 meq/mL; anhydrous monobasic potassium phosphate, KH2PO4, 224 mg/mL; anhydrous dibasic potassium phosphate, K2HPO4, 236 mg/mL.

3. Chemical formulas and weights: KH2PO4, 136.09 g; K2HPO4, 174.18 g.

4. Phosphorus calculation

a. KH2PO4 contribution

b. K2HPO4 contribution

5. Sum of answers for steps 4a and 4b is 3 mmol/mL.

6. Potassium calculation

a. KH2PO4 contribution

b. K2HPO4 contribution

7. Sum of answers for steps 4a and 4b is 4.36 or 4.4 meq/mL.

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*1 mmol of any compound contains 1 mmol of each of its constituent atoms or ions.*
Compounding Compatibility, Stability, and Safety in Parenteral Nutrition

Ning-Tsu Kuo, PharmD, PhD

Abstract
Since the early 1960s, parenteral nutrition (PN) has been used as a primary source of nutrition for patients who are unable to use their gastrointestinal tracts. Over the years, clinical experience and research have improved patient care during nutrition support that includes an interdisciplinary approach to address and closely monitor each patient’s individual nutrition needs. The uniqueness of PN solutions for each patient not only increases the complexity of solution compounding but necessitates that all clinicians, including physicians, dietitians, pharmacists, pharmacy technicians, and nurses, work closely together. The role of pharmacists is especially important in overseeing issues of composition, compatibility, stability, sterility, and safety during PN preparation. Additional issues involve proper storage conditions and intravenous (IV) delivery. This article highlights the chemical properties important for chemical compatibility and stability of PN admixtures and the regulations set by the United State Pharmacopeia (USP) Chapter 797 for personnel and the facility where PN admixtures are compounded. Safety issues related to ordering and compounding PN prescriptions also are addressed and examples of fatal mistakes in units of weight or volume are provided.

Introduction
For more than 50 years, PN has been part of the therapeutic treatment for people who are unable to use their gastrointestinal tracts adequately to meet their nutrition needs (1). A successful PN treatment plan requires collaboration among physicians, dietitians, nurses, and pharmacists. The dietitian works with the physician in assessing the patient’s medical conditions and nutrition needs to produce a PN formula for the pharmacist, who compounds the ingredients into a single bag for IV infusion. A typical PN admixture is composed of amino acids, dextrose, fatty acids, electrolytes (sodium, potassium, calcium, magnesium, phosphate, acetate, and chloride), trace elements (chromium, copper, manganese, selenium, and zinc), multivitamins, water, and often other additives. Because each ingredient has unique physical and chemical properties, mixing all of them together might result in precipitation or emulsion destabilization (2). Therefore, the compatibility and stability of the ingredients must be carefully evaluated before compounding a PN formulation.

Contributing factors to precipitation or destabilization include amino acid concentration, pH of the formulation, dextrose concentration, concentration of the electrolytes, order of mixing, temperature during mixing, storage temperature, and calcium salt used (3). A PN formulation can be prepared either manually or by a computerized automated compounder, although an automated compounder is preferred because of its efficiency and accuracy (4). To ensure absolute sterility in preparing IV infusion products, the USP Chapter 797 sets quality standards for personnel and the facility where compounding sterile products are made, stored, and packaged (5). The purpose of this article is to describe compatibility and stability issues related to PN compounding and to address safety issues in compounding PN at health care facilities.

Compatibility and Stability
Calcium and Phosphate
The most important issue to consider in compounding PN solutions is the possibility of forming a calcium-phosphate precipitate, which could occlude microvasculature and be potentially fatal (6). The risk of developing calcium-phosphate precipitation increases

| Table 1. Factors Affecting Calcium-Phosphate Precipitation |
|----------------|---------------------------------|----------------|
| Factor         | Ideal Conditions to Avoid Precipitation | Factors to Avoid |
| pH             | 2-in-1 formulation: pH 4.5 to 7 3-in-1 formulation: pH 5.4 to 6.5 | 2-in-1 formulation: pH >7 3-in-1 formulation: pH >6.5 |
| Calcium salts  | Calcium gluconate | Calcium chloride or calcium acetate |
| Mixing temperature | Room temperature, 25.0°C | Other than room temperature |
| Mixing order   | Add calcium gluconate as the last ingredient in compounding formula | |
| Final concentration of amino acids and dextrose | Final amino acid concentration between 2% and 6% Final dextrose concentration between 4% to 25% | Final amino acid concentration >6% and <2% Final dextrose concentration >25% and <4% |
| Total concentration of calcium and phosphate salts | Calcium salt (mEq/L) x phosphate salt (mEq/L) product ≤200 | Calcium-phosphate product >200 |
| Presence of other additives | Any additives that might increase pH to >7 in 2-in-1 formula and >6.5 in 3-in-1 formulation | |
with the following factors: 1) high pH, 2) use of calcium chloride instead of calcium gluconate, 3) high temperature of solution, 4) improper mixing order in preparing PN solution, 5) insufficient final concentration of amino acids and dextrose, 6) high concentration of calcium and phosphate salts, and 7) presence of other additives such as lipid emulsion (Table 1) (7).

The amino acid is the primary factor determining the final pH of a PN solution (8). Several commercial amino acid mixtures are available, and each differs in composition, pH, and calcium-phosphate solubility curve. Calcium-phosphate solubility curves were generated by plotting the maximum concentrations of calcium and phosphate using different commercially available amino acid products at room temperature. Some products, such as FreAmine® (B. Braun Medical, Inc, Irvine, CA), contain intrinsic phosphate, which is an important contributor to potential calcium-phosphate precipitation. Calcium gluconate is preferred over calcium chloride. Calcium chloride has a solubility of 74.5 g/L water at 20.0°C, while calcium gluconate has a solubility of 30 g/L water at 20.0°C (9). A desirable calcium salt should have less ionized calcium in a PN solution, and calcium chloride has more than twice the amount of ionized calcium in 1 L of water than calcium gluconate at 20.0°C. Less ionized calcium in a solution reduces the chance of such ions colliding with phosphate molecules to form precipitates. The same logic applies to high temperature. A higher temperature of PN solution increases the dissociation of calcium and phosphate, which combine and precipitate out of solution (10).

The mixing order in preparing a PN solution is also important for inhibiting calcium-phosphate precipitation. Calcium gluconate should be added to a PN admixture after all other ingredients have been mixed (11) to reduce dissociation of calcium gluconate into free ionized calcium and gluconate. At the Cleveland Clinic Home Care (CCHC) Infusion Pharmacy, where more than 100 PN bags are mixed daily, phosphate salt is added as the fifth ingredient and calcium gluconate is added as the last ingredient.

The final concentration of amino acid and dextrose can affect the formation of calcium-phosphate precipitate, largely due to the influence of pH of the PN solution. A lower amino acid concentration means a higher pH that, in turn, means lower solubility of calcium-phosphate. A final concentration of amino acid below 2% is not recommended; the final amino acid concentration should be between 2% and 6% (12). Higher final concentrations of dextrose not only can lower pH but also can increase viscosity, which can have a positive impact of slowing molecule collision between calcium and phosphate (13). Table 2 describes a method of calculating final concentrations of amino acid, dextrose, and lipid in a total nutrient admixture (TNA) solution.

Formation of calcium-phosphate precipitate is directly related to the total concentration of both calcium and phosphate salts. Calcium-phosphate solubility product has been used as a general guideline in PN formulation to predict the possibility of calcium-phosphate precipitate formation (14). A simple formula is used for calculation: calcium salt (mEq/L) x phosphate salt (mEq/L) = calcium-phosphate solubility product. At the CCHC Infusion Pharmacy, a calcium-phosphate solubility product of 200 is the first step to avoid precipitation. Calcium-phosphate solubility product has been used as a general guideline in PN formulation to predict the possibility of calcium-phosphate precipitate formation (14).

In summary, the most important limiting factor in calcium-phosphate precipitation is the total concentration of calcium salt and phosphate salt. Restricting the calcium-phosphate solubility product to less than 200 is the first step to avoid precipitation. TNA destabilization progresses through four stages (18). Stage I is creaming, in which triglyceride particles accumulate at the top of the emulsion. This stage is generally reversible by gentle agitation. Stage II is aggregation, which occurs when triglyceride particles in the creaming stage are too large to be redispersed within the emulsion. Stage III is coalescence. In this stage, triglyceride particles fuse, enlarging the size of particles. In stage IV, which is called cracking, the aqueous and oil phases separate permanently. At stage I, the TNA bag still is safe for infusion following gentle agitation to redisperse the lipid droplets. Once aggregation occurs (stage II), the TNA bag is no longer safe to use. The TNA formula must be reevaluated carefully and adjustments made to avoid any factors that might contribute to the destabilization. Another possible method to avoid TNA destabilization is to infuse the lipid solution in a piggyback bag with a Y-site device along with 2:1 PN solution.

### Table 2. Example of Calculating Final Percentage of Amino Acid, Dextrose and Lipid in Total Nutrient Admixture Solution

<table>
<thead>
<tr>
<th>Total Solution Bag Volume per Bag = 3 L</th>
<th>Final Concentration (g/L)</th>
<th>Final Percentage per Bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid per bag = 90 g</td>
<td>90/3 = 30 g/L</td>
<td>30/1,000 x 100% = 3%</td>
</tr>
<tr>
<td>Dextrose per bag = 150 g</td>
<td>150/3 = 50 g/L</td>
<td>50/1,000 x 100% = 5%</td>
</tr>
<tr>
<td>Lipid per bag = 100 g</td>
<td>100/3 = 33.3 g/L</td>
<td>33.3/1,000 x 100% = 3.33%</td>
</tr>
</tbody>
</table>

### Destabilization in Total Nutrient Admixture

Adding lipid emulsion to a PN solution in a single compartment is frequently referred to as 3-in-1 (3:1) or TNA. Commercially available lipid emulsions consist of soybean oil triglycerides or a combination of both soybean and safflower oil. Using egg phospholipid as the emulsifier allows formulating 10%, 20%, and 30% weight by volume oil-in-water emulsions. The resulting chylomicron-like particle exhibits an inner core of triglyceride covered by the hydrophilic portion of phospholipids that carries negative charges on the surface. Electrostatic repulsion maintains the integrity of lipid emulsion (17). Thus, any factor that disrupts such electrostatic repulsion can result in destabilization of the TNA.
Possible factors that may contribute to destabilization of TNA include: 1) pH of TNA, 2) final concentration of amino acid and dextrose, 3) final concentration of lipid, 4) compounding sequence, 5) electrolyte concentration, 6) other additives, and 7) storage temperature (19).

The challenge of keeping TNAs stable resides primarily with the final pH of the formula. Because lipid emulsion carries negative charges on the phospholipid, the integrity of the emulsion state can be disturbed simply by lowering the pH to below 5 or through the presence of cations. As the solution becomes more acidic, more hydrogen ions become available to bind to the negative charges on the phospholipid, compromising the electrostatic repulsion state. In a TNA formula, amino acids not only have a major role in determining the final pH, but they provide a buffering capacity through a unique isoelectric point. Each amino acid molecule has a positive charge on one end and a negative charge on the other, called zwitterions. The presence of both a positive charge and a negative charge in the same molecule of the amino acid strengthens the integrity of a lipid emulsion (20). The desired pH of a TNA should be in the range of 5.4 to 6.0 (21). Unlike the TNA solution, the pH for PN (2:1) formulation is largely correlated with the pH of the selected commercial amino acid solutions, which range from 4.5 to 7 (8).

The final concentration of amino acid and dextrose is crucial to keeping the lipid emulsion stable. If the final concentration of amino acid is less than 2% in TNA, the pH is higher than 6.5, and the buffering capacity provided by the amino acid solution is minimal, the risk for lipid destabilization increases. As mentioned earlier, a higher final concentration of dextrose in PN solution increases the viscosity, thereby enhancing lipid stability. Furthermore, the pH for dextrose solution is about 4.0. Therefore, a higher dextrose concentration can compensate for lower amino acid content in a formula that has a low final amino acid concentration but a much higher final dextrose concentration. The recommended final concentration of amino acid is between 20 and 60 g/L at the CCHC Infusion Pharmacy, and the final dextrose concentration is 40 to 250 g/L (Table 3).

The final concentration of the lipid emulsion is also important in TNA stability. If the final concentration is less than 2%, the TNA preparation tends to be unstable due to the dilution effect of the emulsifier. Based on the information provided by Baxter Inc., the CCHC Infusion Pharmacy uses lipid emulsion with a final concentration between 20 and 60 g/L in TNA. As with calcium and phosphate, the order of the compounding sequence can be a factor in TNA stability. Lipid emulsion is added before amino acids and dextrose. The rationale is that the amino acid solution provides a buffering effect for the lipid emulsion, thereby strengthening its electrostatic repulsion state (20). Because the negative charge on phospholipid is the primary force of stability, cations are potentially capable of neutralizing the negative charge on phospholipids. Divalent cations such as calcium and magnesium are of great concern in TNA preparation. The nutrition support team at the Cleveland Clinic sets the upper limit of calcium plus magnesium to 20 mEq/L or less based on the lipid manufacturer’s recommendation. Trivalent compounds such as iron dextran are contraindicated in TNA because they can neutralize the negative charge on phospholipid, but iron dextran is compatible with the PN solution. Table 3 describes acceptable ranges of amino acid, dextrose, lipid, calcium plus magnesium, and calcium-phosphate product in TNAs.

Finally, a storage temperature that is either higher or lower than refrigerator temperature might compromise TNA stability via the breakdown of lipid emulsion (6). TNA bags should not be placed in freezers because ice crystals might disrupt the phospholipid barriers, and increases in solute concentration during slow freezing could cause precipitation. Therefore, TNA should be stored in the refrigerator at 4.0°C and never frozen. According to USP 797, PN and TNA bags are safe for 7 days from the day they are compounded if they are stored in the refrigerator between 2º and 8ºC (6). Both PN and TNA bags should be removed from the refrigerator and warmed at room temperature for 2 to 3 hours before infusion. When lipid is being infused via a Y-site device, it is only safe for 12 hours at room temperature, according to Centers for Disease Control and Prevention (CDC) guidelines (22).

### Compatibility With Medications
In addition to the standard ingredients mentioned previously, other medications, such as multivitamins, insulin, famotidine, heparin, ranitidine, vitamin K, octreotide, and methylprednisolone, are added to the PN or the TNA bag before infusion. Based on the information provided from the Handbook on Injectable Drugs (23) and King Guide to Parenteral Admixtures (3), many other medications are compatible with PN or TNA infusion when administered via a Y-site device, such as cefazidime, clindamycin, and diphenhydramine (3). When no literature is available regarding medication compatibility with PN solution, no assumptions should be made.

### Safety
Safety in compounding PN starts with the writing of a PN prescription. A PN order should be clearly legible, with minimum calculations for converting between units. A very good example of a PN Physician Order Form is included in Safe Practices for Parenteral Nutrition from the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) (6). Incorrect conversions between units is the most common overall mistake in hospitals (24). Two recent cases related to PN compounding highlight the safety issue.

(Continued on next page)
Case 1: Converting Milligrams of Calcium Gluconate to Milliequivalents. In April 2011, The Institute for Safe Medication Practice (ISMP) published a report of an infant who died from cardiac arrest due to sodium overdose from his PN solution (25). The original order asked for 14.7 mEq of sodium chloride and 982 mg of calcium gluconate. The pharmacy technician misread the order as 982 mEq sodium chloride and 14.7 mEq calcium gluconate. The pharmacist did not catch the mistake and the nurse failed to recognize the mistake. If the units of electrolytes were all unified as milliequivalents (14.7 mEq of sodium chloride and 4.5 mEq of calcium gluconate), the mistake might not have been fatal. The incorrect reading of units of measure with electrolyte would have been 4.5 mEq of sodium chloride and 14.7 mEq of calcium gluconate, which would have lessened the severity of the mistake.

This incident highlights a pressing safety issue associated with PN orders. In the same publication, ISMP called for a standardized PN order as the top recommendation to avoid a mistake such as that reported. A standardized PN form using grams for amino acid and dextrose, milliliters for lipid, and milliequivalents for all electrolytes or trace element such as zinc chloride was an unusually large quantity for an order. The floor nurse did not match the initial physician order with the pharmacy label on the zinc chloride bag. The mistake was not identified for 3 hours, and the patient died of cardiac failure due to zinc overdose. This mistake highlights the urgency of setting a standardized ordering form for PN, TNA, and IV fluid orders. Knowing the maximum daily doses for electrolytes or trace element such as zinc chloride in adult and pediatric patients is important for ensuring medication safety.

Another reported mistake in compounding PN is confusion between heparin and insulin, which has resulted in death (27). The United States Food and Drug Administration (FDA) and ISMP have compiled a list of high-alert medications, which includes insulin, hypertonic sodium chloride, potassium chloride, potassium phosphate, and magnesium sulfate. One approach to avoid confusion in reaching for the wrong bottles when compounding PN solutions is to minimize the number of different strength stock solutions and separate or color-code different strength stock solutions. ISMP has compiled a list of error-prone abbreviations, symbols, and dosage designations (28). Two abbreviations in the list that are most relevant to PN formulating are U and µg. ISMP recommends substituting Unit and mcg for U and µg. For dose designation, they recommend not using trailing zeros for whole number doses (e.g., write 1 mg instead of 1.0 mg). They also recommend using a zero before a decimal point when the dose is less than a whole unit (e.g., .5 mg rather than .5 mg).

Automated Compounder

Because a typical PN solution contains at least 10 to 15 ingredients, mixing it manually into a single bag has the potential for many mistakes. An automated compounder can remove much of the human error. Accuracy in the automated compounder relies on bar coding computer technology and a mechanical pump that delivers a specific volume based on the number of revolutions. Using bar coding technology, a PN order is scanned and sent electronically to a compounder, which eliminates possible transcription errors that can occur with manual data entry. At least 20 ports are available in a compounder for handling 20 ingredients. Each ingredient is assigned a specific port with a designated bar code. This step allows for temporal separation of incompatible ingredients, thus reducing the chance of calcium and phosphate precipitating. Each bottle of stock solution already has its own National Drug Code (NDC), and scanning the NDC number and matching the correct port assigned through bar code scanning further ensures the accuracy of source solution identification.

The mechanical pump in an automated compounder can deliver a single ingredient within ±3% of requested volume as long as the needed ingredient volume for compounding is greater than 1 mL. The smallest volume an automated compounder can deliver is 0.2 mL. To ensure the accuracy of a volumetric pump further, an independent weight scale is used to check the final volume pumped. This double-fault protection mechanism is inherently designed in an automated compounder, making the PN compounding process accurate and consistent (4). Even though an automated compounder is superior to manual compounding, errors still are possible if policies for the entire process are not carried out vigilantly by
the pharmacy. The most significant disadvantage of an automated compounding device is its cost. The American Society of Health-System Pharmacists (4) published a guideline that included specific objectives related to cost justification:

- Enhanced efficiency and worker safety ... and patient safety with PN use.
- Reduction in labor associated with manually compounded PN admixtures.
- Reduction in waste through more efficient use of base solutions and additives.

If a health facility has a high PN patient census, minimizing or eliminating the possibility of medication errors and improving efficiency in overall costs for labor and materials can justify the long-term cost of an automated compounding device.

Sterility, USP 797
One of the biggest concerns for patients who receive PN is infection. The most common infection in patients receiving PN is catheter-related bloodstream infection; rarely is infection due to PN solution contamination. However, ISMP recently published a report on an outbreak of Serratia marcescens bacteremia in 19 patients who all received PN from a compounding pharmacy in Alabama in March 2011 (29). Nine of the affected 19 patients died. The Alabama Department of Public Health (ADPH) and the CDC found traces of S marcescens in the compounding room at the pharmacy. The pharmacy has stopped all production and recalled all compounded preparations. This incident highlights the danger of inadvertently introducing pathogens into PN bags during the compounding process.

Absolute sterility must be maintained in IV rooms used for compounding PN. To achieve the sterility goal, the USP issued General Chapter 797 Pharmaceutical Compounding-Sterile Preparations regulations in 2004 that were revised in 2008. The regulations apply to all persons who compound sterile preparations and all places where such preparations are compounded, stored, and transported (5).

Specifically, every person who works in the IV room must be properly trained and able to demonstrate good aseptic techniques such as gowning, gloving, and hand washing. Each facility must develop an action plan that includes written procedures to standardize daily tasks such as gowning, gloving, and hand washing. In addition, quality assurance procedures such as sampling protocols, spill cleanup, personnel training, and regular maintenance logs must be well defined and documented.

Each day, before compounding, pharmacy personnel must clean countertops, shelving, vents, anteroom sinks, and storage bin surfaces using 70% isopropyl alcohol. Trash in the IV room must be cleared out twice daily. Sharps containers with needles and syringes and biohazard containers with chemotherapeutic wastes also need to be cleared out twice daily. By the end of the day, floors must be thoroughly cleaned. Every month, IV rooms, anterooms, walls, ceilings, and storage shelving must be cleaned using the procedures for cleaning a surgical suite.

Monitoring sterility for both airborne and surface area contaminants is another important part of USP 797. Using International Organization for Standardization (ISO) as a guide, USP 797 sets different standards for the number of particles per cubic meter allowed in different areas of an IV room. For example, areas where the actual compounding occurs, such as the hood area, are designated as ISO 5 air environment and the allowed particles are no greater than 3,520 particles/M3. Supporting areas could be classified as ISO 7 or 8 air environment, with allowed concentrations of 10,000 particles/M3 and 100,000 particles/M3, respectively. To ensure that air particles circulating in the clean room contain no contaminants from the external environment, USP 797 requires the clean room to be have negative pressure and to have all entering air passed through a high-efficiency particle air (HEPA) filter.

USP 797 recommends the use of contact plates or swabs to take surface samples from all ISO-classified air environments. Two tests are recommended for testing aseptic technique of personnel operating in the IV room: media-fill test and gloved finger test. Both tests are designed to detect any weakness in aseptic knowledge and technique.

Although seemingly tedious, all of these regulations and standards are absolutely necessary for ensuring patient and worker safety. The challenge for the CDC and ADPH is to identify which step or procedure was skipped or missed at the previously cited pharmacy that led to S marcescens contamination in PN bags, resulting in nine deaths.

The FDA is the federal agency that is designated to enforce USP 797 in each health care facility. However, the FDA defers such authority to individual states for regulation and inspection. Some state boards of pharmacy adopt USP 797 fully, but other states only adopt USP 797 partially. The interests of public safety would be best served by universal adoption of USP 797.

Summary
Compounding PN solutions is a complex and complicated process that has inherent safety risks and a very low margin for mistakes. The health care team, including physicians, dietitians, pharmacists, and nurses, must work together to deliver optimum care. Each team member must be vigilant about avoiding harms that might occur during PN order writing, PN formula compounding, or PN solution infusion. Physicians, dietitians, and pharmacists should check every PN formula for compatibility, stability, and safety.

Ning-Tsu Kuo, PharmD, PhD, is a staff pharmacist at Cleveland Clinic Home Infusion Pharmacy, Independence, OH.

References
4. American Society of Health-System Pharmacists. ASHP guidelines on the safe use of automated compounding devices for


Chair’s Column

(Continued from page 2)

DNS was also very proud to recognize David Frankenfield, MS, RD, chief clinical dietitian, Penn State Milton S. Hershey Medical Center, Hershey, PA, for winning ADA’s prestigious Excellence in Practice-Dietetics Research Award. DNS nominated David for his diligent and thorough research in predictive energy requirements, which led to the development of the Penn State equations. No doubt every nutrition support dietitian is familiar with his work. Very hearty congratulations to both David and Dr. DeLegge.

Our Spotlight Session was a huge success, with Kathy Barco, RD, CNSC, and Neha Parekh, MS, RD, CNSC, presenting Navigating Intestinal Surgery: How to Access and Feed the Altered GI Tract. They had a packed room and stayed long afterward to answer questions from attendees. We were also involved in the pre-FNCE workshop Documenting Severe and Non-Severe Malnutrition: A Hands-On Approach. This session was a joint effort of ADA’s Coding and Coverage Committee Malnutrition Workgroup and DNS. Jane White, PhD, RD, FADA, Bob DeChicco, MS, RD, CNSC, and I were the speakers, with Ainsley Malone, MS, RD, CNSC, as moderator. We had several break-out assistants, including Jennifer Wooley, MS, RD, CNSC, Louise Merriman, MS, RD, CDN, Teresa Scollard, MBA, RD, LD, and ADA staff members Marsha Schofield, PhD, RD, and Mara Bujnowski, MAEd, RD. I especially appreciated the engaged participants from this session and their recognition of the importance in determining a consistent definition of malnutrition.

For those DNS members who plan to attend A.S.P.E.N.’s Clinical Nutrition Week, January 21-24, 2012, in Orlando, FL, we hope to see you at the DNS sessions on Tuesday, January 24, Abdominal Assessment and Interpretation of Abdominal Radiography for Feeding Tube Placement and Handgrip Dynamometry and Interpretation of Radiography for Central Line Placement. Please stop by our booth in the exhibit area as well.
Compounding Parenteral Nutrition: Reducing the Risks
Caitlin Curtis and Gordon S. Sacks
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What is This?
Compounding Parenteral Nutrition: Reducing the Risks

Caitlin Curtis, PharmD, BCNSP¹; and Gordon S. Sacks, PharmD, BCNSP, FCCP²

Financial disclosure: none declared.

Compounding parenteral nutrition, either manually or with an automated compounding device, requires aseptic conditions and trained personnel. The revised version of United States Pharmacopeia Chapter <797> is a comprehensive document that describes standards and procedures to minimize the risk of contamination of compounded parenteral products. The chapter includes evidence-based instructions for pharmacy design, washing, garbing, cleaning, quality assurance, and personnel training and evaluation designed to improve compounding practices in all pharmacies that compound parenteral products. Because parenteral nutrition is a compounded product mixed from multiple additives, it is important to maintain these standards, especially when using an automated compounding device. This article is an overview of United States Pharmacopeia Chapter <797>, with special emphasis on parenteral nutrition. (Nutr Clin Pract. 2009;24:441-446)

Keywords: parenteral nutrition; parenteral nutrition, total; pharmaceutical preparations; drug compounding; drug packaging

The production of fluids for intravenous use is optimally performed in an aseptic environment, and the finished product should be free of microbes, spores, endotoxins, chemical contamination, and physical matter. Compounding such a product requires trained personnel, an adequate environment, and effective technique.¹ However, over the years there have been many reports of contaminated intravenous compounds, including contaminated parenteral nutrition (PN).²⁻⁵ PN is especially at risk of contamination because it is a mixture of multiple additives and is an excellent growth medium for microbes.

The United States Pharmacopeia (USP), a nongovernmental, nonprofit healthcare organization, is charged with developing national standards for drug purity and safety for all prescription and over-the-counter medicines manufactured or sold in the United States. These standards are published in a book, the United States Pharmacopeia: National Formulary (USP-NF), and healthcare practitioners not familiar with its organization need to understand the significance of each chapter number. Book chapters numbered ≤999 are regarded as medication standards that must be followed and are enforceable by the U.S. Food and Drug Administration (FDA). Those book chapters numbered 1000-1999 are considered informational, whereas chapters assigned numbers ≥2000 are related to nutrition supplements. Because of a low compliance with voluntary guidelines, the USP became involved with issuing standards on the pharmaceutical compounding of sterile products. An expert committee of USP drafted Chapter <797>, the first official monograph enforceable by regulatory agencies concerning the procedures and requirements for pharmacy-prepared sterile products, and it became the official minimum standard in January 2004. Much of the same information was previously published as recommendations in the nonenforceable Chapter <1206>, which focused on dispensing for home care and guidelines related to sterile product preparation published by the American Society of Health-System Pharmacists (ASHP).⁶ Although Chapter <797> discusses standards applying to all sterile dosage forms that are compounded, only information pertinent to PN and its implications are reviewed here.

Preparation of PN falls under the category of a compounded sterile preparation (CSP) by the definition of USP Chapter <797>.¹ The revised version of USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparation, was released in December 2007 and became official on June 1, 2008. The chapter describes new safety standards for facilities that compound sterile products in an attempt to improve production practices and reduce the risk of contamination. All compounding areas have defined levels of cleanliness and limits of particulate matter, which are defined by International Standards (ISO) Classifications. Table 1 provides these classifications. USP Chapter <797>...
is an official document of the USP-NF and is therefore enforceable by the FDA. Because the FDA allows individual states to regulate the practice of pharmacy, it is usually up to the state board of pharmacy to adopt the standards and inspect pharmacies for compliance. However, the FDA does have the power to inspect pharmacies and enforce the standards in the interest of public health. Medication recalls and additional legal sanctions can occur upon failure to comply with USP standards.

Compliance with the USP Chapter <797> standards may require multiple changes in the way that pharmacy personnel operate while preparing CSPs. The standards describe in detail the environments for preparation of sterile products, cleaning of equipment and surfaces, personnel training, washing and garbing procedures, and quality assurance checks. This article summarizes the new standards and also outlines the specific sections which pertain to compounding PN.

### Table 1. Risk-Level Classification and Beyond-Use Dating Guidelines for Compounded Sterile Preparations

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Examples</th>
<th>Beyond-Use Dating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Reconstitution of a single-dose vial of lyophilized powder with sterile diluents for transfer into another container (eg, pediatric multivitamins)</td>
<td>Room (20°-25° C) 48 h, Refrigeration (2°-8° C) 14 d</td>
</tr>
<tr>
<td>Medium</td>
<td>Mixing of multiple manufactured additives for transfer into a large-volume parenteral solution (eg, PN formulations)</td>
<td>30 h, 9 d</td>
</tr>
<tr>
<td>High</td>
<td>Preparation of nonsterile powder for intravenous infusion (eg, extemporaneously compounded L-glutamine for supplementation in a PN formulation)</td>
<td>24 h, 3 d</td>
</tr>
</tbody>
</table>

PN, parenteral nutrition.

### Table 2. ISO Classification of Particulate Matter in Room Air (Limits Given in Particles of ≥0.5 mcm/m³)

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Particle Limit per m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>35.2</td>
</tr>
<tr>
<td>4</td>
<td>352</td>
</tr>
<tr>
<td>5</td>
<td>3,520</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
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</tbody>
</table>


### Pharmacy Design

USP Chapter <797> outlines a 3-tiered approach for assigning the potential risk of contamination associated with compounding of CSPs (Table 2). PN is classified as a “medium-risk-level” CSP when it is prepared from crystalline amino acids and commercially available monohydrated dextrose, injectable lipid emulsions, electrolytes, multiple vitamins, trace elements, and sterile water. It carries a higher level of risk because it requires the mixing of multiple small doses of different sterile products into 1 large bag. When PN is compounded using powdered amino acids, it is classified as a “high-level” CSP because its preparation involves the use of nonsterile ingredients and carries the highest risk for contamination by microbial, chemical, or physical matter. As a result, high-risk-level CSPs must undergo some type of sterilization process prior to administration. All risk-level compounds should be prepared in an environment in which particulate matter and microorganisms are minimized, and the air quality must meet certain standards. Pharmacies must be designed specifically to meet these standards, which require an anteroom and a buffer area to separate the general environment from the area of compounding. The lower the number of classification, the cleaner the air must be. The anteroom is an area where personnel can perform washing and garbing procedures prior to entering the compounding area, and it must meet ISO class 8 requirements. After personnel have garbed and washed, they must enter the buffer area. The buffer area must be kept as clean and as free of particulates as possible, because this is the area
where products are gathered directly before compounding takes place. All materials in this area, including furniture, equipment and supplies, must be nonpermeable, nonshedding, cleanable, and resistant to damage by disinfectants. All materials should be cleaned and disinfected before entering the buffer area. Finally, the cleanest area must be the area where compounding occurs, called the direct compounding area (DCA), which must meet ISO class 5 standards. The DCA airflow must be controlled by 1 of the following devices: laminar airflow work benches, biological safety cabinets, compounding aseptic isolators, or compounding aseptic containment isolators.

All areas should be constructed so that the space minimizes dust and dirt collection. Counters, shelves, and carts should be constructed of smooth, nonporous, nonshedding materials such as stainless steel or molded plastic that are able to be cleaned and disinfected on a regular basis. Walls and ceilings must be constructed of nonporous materials, such as heavy-gauge polymer or epoxy-coated gypsum board. Other fixtures, such as hanging light fixtures or pipes, should be minimized.

Anterooms are to be free of food, drinks, and materials that have been exposed to patient care areas. In the anteroom, all package compounding supplies, including needles, syringes, tubing sets, and small- and large-volume parenteral products, must be taken out of cartons and wiped with sterile 70% isopropyl alcohol before they are transferred to the buffer area. An apparent demarcation must separate the anteroom and the buffer area, whether it is a line on the floor or a physical separation, such as a door.

Cleaning and Garbing Procedures

To maintain ISO class 5, 7, and 8 standards, personnel must strictly adhere to washing and garbing procedures before entering the areas. First, in the anteroom, before entering the buffer area, personnel should remove all outer garments and any hand, wrist, or ear jewelry. Next, personnel should put on appropriate garb, in the following order: shoe covers, head covers, and face masks. Personnel should wash hands and forearms with soap and water for 30 seconds and dry with lint-free disposal towels or electronic hand dryer. After the hand-cleansing procedure, personnel should put on a nonshedding gown with cuffs at the wrists and closure at the neck. They may enter the buffer area after appropriate garbing and must use waterless alcohol-based surgical hand scrub to clean their hands before donning sterile, powder-free gloves. Gloves should be kept clean throughout the day by wiping or rubbing 70% isopropyl alcohol to all surface areas of the gloves, and this cleansing should take place after the gloves make contact with any nonsterile surface.

After personnel have finished with cleansing and garbing procedures, they should begin cleaning the work area. Personnel should clean and disinfect surfaces in the primary compounding area at the beginning of every shift, before a new batch is started, every 30 minutes during continuous compounding, when there are spills, and when known contamination is present or suspected. Counters and floors must be cleaned daily with nonshedding wipers and mops dedicated to each area. For instance, sponges used to clean the buffer area should stay in the buffer area. Cleaning elements should be disposable if possible. If cleaning elements are not disposable, then they should be cleaned by standard procedures on a regular basis. Walls, ceilings, and shelving must be cleaned monthly. All cleaning should be done by trained personnel with approved cleaning and disinfecting agents.

To maintain ISO standards, it is important to avoid extraneous particles and microbes. All supplies brought into the buffer area must be removed from cardboard cartons in an anteroom before being passed into the buffer area in order to minimize airborne particulates. To decrease microbial contamination, all supplies including needles, syringes, tubing sets, vials, and small- and large-volume parenteral products should be cleaned and disinfected with sterile 70% isopropyl alcohol before being transferred to the buffer area. All equipment that is brought into the buffer area must be cleaned and disinfected, including carts and storage containers.

Personnel Training and Evaluation

To be compliant with USP Chapter <797>, institutions must show that all personnel are trained in garbing procedures, aseptic work practices, and cleansing/disinfection procedures. Institutions must document that personnel complete didactic training, pass written competencies, and undergo skill assessment using observational audit tools and media-fill testing. Annual documentation of successful completion of written and media-fill testing is required for all personnel who perform low- and medium-risk–level compounding, and semiannual documentation is required for personnel who perform high-risk–level compounding. Appendices in USP Chapter <797> provide excellent tools for assessment of procedures by direct observation.1 To ensure proper hand hygiene, garbing procedures, and cleaning and disinfection procedures, a pharmacy supervisor directly observes the compounding personnel while they perform the procedure. To pass the aseptic technique competency, compounding personnel must pass both a direct observation test and a media-fill test. Media-fill testing assesses the quality of aseptic technique and provides objective evidence of production of a sterile product. To pass this competency, personnel use commercially available sterile fluid culture media, such as soybean casein digest medium, to simulate a drug product for compounding. If the medium is not transferred from 1
container to another aseptically, bacteria will grow and will be visibly turbid. For successful completion, the compound must be incubated and must not be turbid for 14 days after manipulation. Compounding personnel who fail written or observational assessment, or whose aseptic technique results in contamination, must be retrained and retested until they pass all portions of assessment.

Quality Assurance

All of the compounding and associated areas must be tested periodically to prove that the areas meet particulate and cleanliness standards. Except for pressure differentials, this environmental sampling should occur and be documented as part of the certification of new facilities or equipment as well as for recertification, which should occur every 6 months. Environmental sampling should also occur after any equipment is serviced and after physical changes have been made to the area (eg, new construction, rearrangement). Sampling must occur in response to patient-care-related infections when the sterile product area may be at fault or in response to suspected suboptimal work practices of compounding personnel.

The environment should be sampled for airflow between areas, nonviable particulates, and viable particulates (viable refers to microorganisms). Airflow should be measured between the buffer area and the anteroom, and between the anteroom and the general environment outside the anteroom. Airflow should be monitored and documented at least every work shift. Nonviable and viable particulates are measured less often, as stated previously. Nonviable particulates are measured to make sure that the various levels of cleanliness are being maintained by the devices that maintain ISO class 5 environments. Viable particulates are measured in select sampling sites to ensure the lowest levels of antimicrobial invasion into the compounding area. Sampling sites should include areas of the greatest risk of contamination, such as work areas near passageways or counters located in an area of high air turbulence. The chapter outlines in detail the materials needed for testing, including viable air sampling devices, type of agar or growth medium plates, and incubation conditions and time.

Environmental sampling should be part of the standard operating procedure of the pharmacy. As such, the procedure for measuring and documenting environmental sampling should include a sampling plan that defines acceptable limits for pressure gradients and nonviable and viable particles. The plan should instruct pharmacy personnel on what steps to take if the samples exceed the acceptable limits.

Quality Assurance for PN Compounding

It has been estimated that 65% of all PN admixtures in the United States are prepared with automated compounding devices (ACDs), a practice that is permissible under USP Chapter <797> standards. Guidelines for ensuring the accuracy and precision of ACDs are addressed in this chapter. Compounding personnel should test the device for accuracy on a daily basis, document the results, and then review the results weekly. Personnel should perform both volumetric and weight testing using sterile water for the fluid test. Other additives may be tested if desired. Additional tests using the hospital laboratory may be used to ensure accurate compounding, such as testing for dextrose or for potassium concentration in the final compounded preparation. Other fundamental elements related to the safe and cost-effective inclusion of this technology into pharmacy operations have been addressed by ASHP guidelines published in 2000. As many as 20 single-source containers are attached to an ACD during PN compounding, all of which are pumped into a single large-volume plastic bag. The order in which individual ingredients are added to the final PN admixture is very important because specific components may be incompatible if added too close together in the sequence (eg, calcium gluconate and sodium/potassium phosphate). Use of the ACD for purposes other than PN compounding should be discouraged because this will likely require reprogramming of configurations and increase the risk for error. Compounder tubing changes must occur at appropriate time intervals in keeping with manufacturer recommendations, or mortality from infected solutions can result. During the course of a work shift, single-source containers may be replaced several times during the compounding process—all of which is performed within an ISO class 5 environment. Strict aseptic practices must be followed by the pharmacist during these changes of additive source containers to reduce the risk of contamination. Minimum performance standards for quality assurance of compounding procedures should also be established. If changes in the accuracy of delivering a single additive (eg, potassium chloride) exceed a predetermined percent error, a plan for implementing corrective actions should be in place. All large-volume PN components (ie, amino acids, dextrose, and lipid emulsions) should be acquired from 1 manufacturer unless published data exist to substantiate the safety, compatibility, and stability of alternative final admixture formulations.

Compounding personnel should inspect the physical appearance of the final PN formulation. Although microprecipitates and incompatibilities cannot be seen by the naked eye, large-particle contaminants or precipitates are the most likely to immediately harm the patient, and they can easily be detected before the product is dispensed. For PN formulations without lipid emulsions, the product should be inspected against a dark background for the presence of particulates, such as fibers from alcohol swabs, cores of additive vials, or insoluble precipitates. Compounding personnel should also look for...
any signs of crystallization or for haziness of the product. For PN admixtures with lipid emulsions, compounding personnel should examine the bag for any signs of a cracked emulsion, including separation of components into an oil layer or into fat droplets. Finally, access and use of any ACD equipment for PN preparation should only be available to personnel who have been appropriately trained and demonstrated competency in this area.8

Final Checks and Tests

Labeling

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Safe Practice guidelines outline best practices for labeling PN (Figure 1).10 This format provides the most straightforward way of displaying ingredients in the formulation, as well as other required elements for intravenous compounds, including route of administration, date and time for administration, beyond-use date, dosing weight, and rate. Compounding personnel should have a standard procedure for verifying the contents of the finished product by comparing the finished labeled PN product to the original order.1 The best way is to have a double-checking procedure in place. If additives are added manually to the bag, original containers (ie, vials) should be grouped with the final product; if the entire vial is not used, a syringe pulled back to the volume of the product measured should accompany the vial and the final product.

Storage and Use of PN Admixtures

A beyond-use date should appear on the PN label. A beyond-use date is different from an expiration date. Whereas expiration dates are based on rigorous tests for the chemical and stability of manufactured sterile products, beyond-use dates are based on the risk level of the CSP with consideration given to the time and temperature at which the preparation will be stored. According to USP Chapter <797> standards, a beyond-use date for a PN admixture prepared for inpatient administration is 30 hours based on storage at room temperature and a medium-risk–level (see Table 1). In the home-care environment, the beyond-use date can be extended to 9 days as long as PN admixtures are stored at 2°-8° C (36°-46° F) until use. The 30-hour time limit still applies once PN infusion is initiated.

Summary

Compounding of PN is not without its risks, but the standards outlined in USP Chapter <797> greatly reduce risks of contamination of microbial or particulate matter. Most pharmacies will need to change their physical design to provide space for an anteroom and buffer area surrounding direct compounding areas. Washing and garbing are important steps in maintaining a clean environment, as is regular cleaning with approved agents. Quality assurance tests, including testing of air; aseptic technique; and personnel compliance with standard operating procedures are important to maintain a clean environment with minimal airborne particulates. Although many of these changes may be difficult and expensive to achieve, they will all lead to safer compounding practices and provide the patient with the best end product.

References


6. The ASHP Discussion Guide on USP Chapter <797> for Compounding Sterile Preparations: Summary of Revisions to USP Chapter <797>, developed by the American Society for Health-System Pharmacists in collaboration with Baxter Healthcare Corporation. Bethesda, MD: ASHP, Inc.


