A.S.P.E.N. Parenteral Nutrition Safety Consensus Recommendations

Phil Ayers, PharmD, BCNSP, FASHP-Chairperson1; Stephen Adams, MS, RPh, BCNSP2; Joseph Boullata, PharmD, RPh, BCNSP3; Jane Gervasio, PharmD, BCNSP, FCCP4; Beverly Holcombe, PharmD, BCNSP, FASHP5; Michael D. Kraft, PharmD, BCNSP6; Neil Marshall, RN, BSN, CRNI, CNCS7; Antoinette Neal, RN, CRNI, CNCS, VA-BC8; Gordon Sacks, PharmD, BCNSP, FCCP9; David S. Seres, MD, ScM, PNS10; Patricia Worthington, MSN, RN, CNCS11

Abstract
Parenteral nutrition (PN) serves as an important therapeutic modality that is used in adults, children, and infants for a variety of indications. The appropriate use of this complex therapy aims to maximize clinical benefit while minimizing the potential risks for adverse events. Complications can occur as a result of the therapy and as the result of the PN process. These consensus recommendations are based on practices that are generally accepted to minimize errors with PN therapy, categorized in the areas of PN prescribing, order review and verification, compounding, and administration. These recommendations should be used in conjunction with other A.S.P.E.N. publications, and researchers should consider studying the questions brought forth in this document. (JPEN J Parenter Enteral Nutr. XXXX;xx:xx-xx)

Keywords
parenteral nutrition; nutrition; parenteral formulas/compounding; safety

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Introduction
Parenteral nutrition (PN) serves as an important therapeutic modality that is used in adults, children, and infants for a variety of indications. The appropriate use of this complex therapy aims to maximize clinical benefit while minimizing the potential risk for adverse events. Despite being classified and acknowledged as a high-alert medication,1 only 58% of organizations have precautions in place to prevent errors and patient harm associated with PN.2 Complications can occur as a result of the therapy and as the result of the PN process. These recommendations are based on practices that are generally accepted to minimize errors with PN therapy. However, the broad range of healthcare settings in which PN administration occurs—from critical care to home care—raises the potential for disparities to exist in the knowledge and skills of the healthcare professionals responsible for PN prescribing, review, compounding, and administration. Regardless of the setting or the number of patients treated in a given facility, the classification of PN as a high-alert medication requires healthcare organizations to develop evidence-based policies and procedures related to PN.
Conceptually, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends use of the standardized process, which includes clinicians with expertise in the area of nutrition support.3

During the past few years, many circumstances and incidents have threatened the safety of patients receiving PN as an important therapy. In light of the need to revise A.S.P.E.N.’s Safe Practices for Parenteral Nutrition guidelines and to publicly address the safety of PN prescribing, compounding, and delivery, A.S.P.E.N. leaders hosted a multiorganizational safety summit on September 23, 2011. This summit brought together 46 key stakeholders to identify processes to improve the safety of prescribing, preparing, and delivering PN to patients across a variety of healthcare settings.3 Findings from this summit guided the A.S.P.E.N. PN Safety Task Force to develop safety consensus recommendations.

In an attempt to answer as many questions about PN safety as possible, this Task Force, in partnership with the A.S.P.E.N. Clinical Practice Guidelines Editorial Board PN workgroup, developed many clinical questions still unanswered in existing documents. The workgroups were divided into two segments, each responsible for specific tasks. The first group developed questions that could be answered with a high level of confidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process (the process by which the A.S.P.E.N. Clinical Guidelines are developed).5 The second group developed questions for which the level of evidence in the literature did not support any GRADE-level recommendations, meaning that consensus recommendations would depend on expert opinion. This paper addresses clinical concerns that impact PN safety for which current literature does not provide GRADE-level evidence and provides consensus recommendations for safe PN practice and future research based on expert opinion. These recommendations are not clinical guidelines as defined by A.S.P.E.N.6 The need to deliver practice information to clinicians, even when it is of a consensus nature from practice experts, remains an important role of A.S.P.E.N. Redundancies were deliberately built into this document between sections for users who may only view individual sections based on their practice area. Reviewers of this paper included the A.S.P.E.N. Clinical Practice Committee, Dietetics Practice, Medical Practice, Nutrition Support Nurses, and Pharmacy Practice Sections, as well as clinical content experts outside of the organization. This document was also reviewed and approved by the A.S.P.E.N. Board of Directors. The questions to be answered with the Clinical Practice Guidelines GRADE process, listed in Appendix 1, will be addressed by a separate workgroup and published separately. This document should be used in conjunction with those guidelines.

Similar to A.S.P.E.N.’s Standards of Practice documents, the following terminology is used with each recommendation to indicate the level of evidence and strength of consensus reached for each statement.

“Should”: Indicates that the recommendation is to be followed strictly.

“May”: Indicates a course of action that is permissible within the limits of recommended practice.

The recommendations within this document are intended for discussion and adoption over time by organizations and individual professionals involved in the routine care of patients requiring PN. These recommendations are not intended to supersede the judgment of the healthcare professional based on the circumstances of the individual patient. Although the substantial focus of these recommendations is on institutional settings, many of the safety issues exist across other patient-care settings. Concerns that are unique to home care are also addressed where appropriate. In every clinical setting, it is the responsibility of the prescriber, pharmacist, nurse, dietitian, and nutrition support team to recognize and report all PN-related medication errors, whether or not they reach the patient. This allows the medication safety officer/committee to review and address these events periodically with the committee or individuals having oversight of PN.

References
Prescribing and Communicating the Parenteral Nutrition Order

Background

PN is a complex prescription therapy associated with significant adverse effects. Deaths have occurred when safe practice guidelines were not followed. Appropriate and safe prescribing and ordering of PN is a critical first step and an essential component of the PN use process. The safe prescribing of PN requires a thorough knowledge of protein and energy requirements, macronutrients, micronutrients, fluid homeostasis, and acid-base balance. The prescriber shall be well versed in the appropriate indications for PN, basics in sterility and infection control, as well as vascular access devices (peripheral and central) and their associated complications. Safe prescribing of PN begins with PN-specific interdisciplinary education and institutional policies focused on writing clear PN orders. Furthermore, there shall be clear means of communication among physicians, physician extenders/mid-level providers (eg, nurse practitioners, physician assistants), dietitians, pharmacists, and nurses involved in this process. This section provides guidance and suggestions for healthcare institutions to adopt in order to promote safe prescribing of PN. Many of these recommendations have been adapted from literature of another high-alert therapy: cancer chemotherapy.2–4

Question: Prescribing 1–2 (P1–P2)

(P1) Does a standardized process for PN prescribing increase clarity and reduce PN-related errors? (P2) What are the essential elements of a PN order that minimize errors?

Recommendations

1. Healthcare organizations shall use a standardized process for PN management, and this process shall include clinicians with expertise in the area of nutrition support, preferably from multiple disciplines.5,6
   a. Healthcare organizations shall develop written policies and procedures for all aspects of PN therapy in the manner described in the A.S.P.E.N. Safe Practices for Parenteral Nutrition.1
   b. The patient and caregivers shall be informed of the risks and benefits associated with PN.
   c. A comprehensive PN education program and competency assessment shall be developed for healthcare professionals who are involved in the care of patients receiving PN therapy, and competency should be assessed at least annually.4
   d. Healthcare organizations shall have a written policy addressing credentials, training, and competency certification(s) required of clinicians who prescribe PN.4

2. The primary healthcare team, in collaboration with nutrition support professionals, shall evaluate, clearly define, and accurately document the patient’s medical problem(s) and indication(s) for PN.
   a. The patient shall have an appropriate indication for PN therapy based on published guidelines and evidence for the use of PN, which shall be documented in the medical record.1
   b. The healthcare team shall confirm that the patient has appropriate intravenous (IV) access for PN prior to prescribing PN therapy.1
   c. The indication(s) for PN and appropriate IV access shall be included on the PN order (see section 4 and Table 1).1

3. The primary healthcare team, in collaboration with nutrition support professionals, shall specify and document the therapeutic goal(s) of PN therapy.
   a. Appropriate energy and protein goals shall be determined for the patient’s condition based on published guidelines and evidence.1
   b. Appropriate parameters and frequency of monitoring shall be determined for the patient’s condition to assess efficacy, detect and prevent complications, evaluate changes, and document outcomes.1
   c. Appropriate monitoring parameters for PN shall include fluid requirements, serum electrolyte concentrations, serum glucose concentrations, hepatic function, renal function, serum triglyceride concentrations, and signs or symptoms of vascular access device complications.1
   d. Therapeutic goals should be established for PN, including end points, response to treatment, and treatment failure.

4. PN shall be prescribed using a standardized PN order format and review process applicable to patients of every age and disease state within a healthcare organization.1,6
   a. Standardized electronic PN orders (eg, a computerized prescriber order entry [CPOE] system) should be used to prescribe PN for all patients.1,7–9 Handwritten orders to prescribe PN should be avoided due to potential for error. Verbal and telephone orders for PN should be avoided.
   b. Clinical decision support should be available within electronic PN orders to alert and prevent prescribers from ordering doses of macronutrients, micronutrients, and/or medications that exceed recommended/safe clinical limits or that exceed limits of compatibility (eg, hard limits when maximum concentrations have been exceeded).1,7,8
   c. When a CPOE system is not available, PN should be prescribed using a standardized order
PN order templates shall be designed so they are clear and easily understood by all healthcare professionals involved in the care of patients receiving PN.1

e. Table 1 lists components that shall be included on the PN order.1,4

f. All PN order templates should include the required components listed in the sequence in Table 1. This sequence should match the PN labels as well. See Figure 1 and Figure 2 for PN Order Templates.

g. In the event of a product shortage, PN component conservation and allocation strategies should include the A.S.P.E.N. parenteral nutrition shortage considerations for multivitamins, trace elements, IV fat emulsions (IVFE), amino acids, electrolyte/minerals, and cysteine,10-15 and the PN order format should be updated accordingly. Multivitamins shall be prescribed daily in PN admixtures. When multivitamin products are not available, thiamine, ascorbic acid, pyridoxine, and folic acid should be prescribed daily.10

h. All PN ingredients shall be ordered in amounts per day (eg, for adult patients) or amounts per kilogram per day (eg, pediatric and neonatal patients) rather than in amounts per liter, percent concentration, or volume.1 Amount per day refers to macronutrients in grams per day, and micronutrients in mEq, mmol, mcg, or mg per day. Electrolytes shall be ordered as the complete salt form rather than the individual ion.1 Each individual macronutrient and micronutrient ordered shall be listed with its corresponding dose.1 If available, the total ion amounts and concentrations may be reported or displayed to the prescriber within the PN order.

i. The PN order template in CPOE systems should display current patient monitoring values and their date and time of entry to include parameters such as laboratory values, temperature, weight, etc.

j. The PN order template should contain the full generic name for each ingredient.1,4 Proprietary names should only be used when multiple products exist and/or when the proprietary name may assist in identifying unique properties of the specific dosage form (eg, inherent electrolytes in amino acid formulations, fatty acids in IVFE).4 Any abbreviations shall follow The Joint Commission standards on abbreviations.4,16 Abbreviations on the Institute for Safe Medication Practices (ISMP) list of error-prone abbreviations, symbols, and dose designations shall not be used.17

k. The PN order should include related orders for routine care, laboratory tests, and relevant monitoring parameters.1

l. Prescribing a PN formulation that includes non-nutrient medications should be avoided. When no other reasonable alternatives exist, non-nutrient medications shall only be included on the PN order if data support compatibility/stability.1

m. Healthcare organizations should develop policies and/or protocols to allow modification of PN orders when potential incompatibilities may exist (eg, incompatibilities associated with calcium and phosphate salts, adjustment of IVFE dosing when it is not expected to be stable as a total nutrient admixture [TNA] [ordering IVFE separately or adjusting IVFE dosing such that the daily dose achieves minimum concentration for stability]).1 All PN order modifications shall be communicated to the healthcare team and documented in the medical record. PN orders shall be signed by a licensed prescriber who has been credentialed by the healthcare organization to prescribe PN.4

n. PN orders should be prescribed with a time limitation to allow for appropriate patient evaluation at predetermined intervals based on clinical status and required level of care.1-4

o. For optimal safety, PN orders should be prescribed and transmitted when supported by properly trained personnel who regularly perform this task. This is usually done during daytime hours.18

5. Institutions shall create a home PN order template/format that provides a safe plan for multiple days of therapy. The prescription for home PN therapy should be written in a format that specifically reflects trends in laboratory values and previous days of PN therapy. An institutional daily PN order format should not be used as a home PN prescription.

6. The most appropriate nutrition modality, in collaboration with nutrition support professionals, should be prescribed for the patient. Healthcare organizations should determine the most appropriate types of PN formulation(s) for their patient population(s) (eg, standardized compounded, standardized commercial [pre-mixed] PN products, or customized compounded PN admixtures) or methods of delivery (eg, dextrose/amino acid vs total nutrient admixtures) and should develop criteria for each formulation that will be used in their patients.19
Table 1. Required Components for PN Orders and Preferred Sequence.

<table>
<thead>
<tr>
<th>Components for the PN Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Information</td>
</tr>
<tr>
<td>Patient identifiers (patient name, medical record number or other unique identifiers, birth date/age, patient location)</td>
</tr>
<tr>
<td>Patient location (home address for home PN patients)</td>
</tr>
<tr>
<td>Allergies and reactions</td>
</tr>
<tr>
<td>Height and dosing weight (metric)</td>
</tr>
<tr>
<td>Diagnosis(es)/indication(s) for PN</td>
</tr>
<tr>
<td>Vascular access device/location</td>
</tr>
<tr>
<td>Administration date/time</td>
</tr>
<tr>
<td>PN Ingredients (should match PN label)</td>
</tr>
<tr>
<td>Amino acids</td>
</tr>
<tr>
<td>Dextrose                                     L</td>
</tr>
<tr>
<td>IVFE                                         L</td>
</tr>
<tr>
<td>Sodium phosphate                             L</td>
</tr>
<tr>
<td>Sodium chloride                              L</td>
</tr>
<tr>
<td>Sodium acetate                               L</td>
</tr>
<tr>
<td>Potassium phosphate                         L</td>
</tr>
<tr>
<td>Potassium chloride                          L</td>
</tr>
<tr>
<td>Potassium acetate                            L</td>
</tr>
<tr>
<td>Magnesium sulfate or magnesium chloride        L</td>
</tr>
<tr>
<td>Calcium gluconate                            L</td>
</tr>
<tr>
<td>Multivitamins                                L</td>
</tr>
<tr>
<td>Trace elements                               L</td>
</tr>
<tr>
<td>Additives (e.g., cysteine, regular insulin) as clinically appropriate and compatible</td>
</tr>
<tr>
<td>PN Instructions</td>
</tr>
<tr>
<td>Total volume, infusion rate, start and stop times, cycle information</td>
</tr>
<tr>
<td>Prescriber and contact information</td>
</tr>
</tbody>
</table>

**Rationale**

PN is a complex prescription therapy with many potential safety concerns. The World Health Organization (WHO) advocates a systematic approach to prescribing in order to improve quality and minimize errors. Pollock and colleagues described considering drug costs and using computer technology when prescribing medications. These approaches provide an excellent template for the clinician prescribing PN. The A.S.P.E.N. Safe Practices for PN document describes the benefits of using a standardized PN ordering process and recommends components that should be included on a PN order template (mandatory, strongly recommended, and worthy of consideration). Like PN, chemotherapy is a class of complex prescription medications with critical safety concerns. The American Society of Clinical Oncology and Oncology Nursing Society developed Chemotherapy Administration Safety Standards in the outpatient setting in 2009, with revisions to expand these to the inpatient setting in 2011. The concepts in these safety standards are consistent with the A.S.P.E.N. Safe Practices for PN. We recommend that healthcare organizations and clinicians adopt these standards and guidelines when creating policies for ordering/prescribing PN.

Standardized order formats for PN incorporating prescriber guidelines can provide education that can lead to reduced prescribing errors, improved efficiency/productivity, and ultimately reduced costs and waste. In addition, adopting a standardized PN order format designed with ingredients listed in the same sequence may improve consistency, and clarifying orders decreases the risk of errors when patients transition care from one setting to another. The Agency for Healthcare Research and Quality recently reported on a meaningful reduction in errors (from 9 to 4 per 1000 PN orders) at a children's hospital that adopted a standardized ordering and administration process for PN. Other observations included a reduced need for pharmacists to correct orders, a more efficient ordering and administration process, earlier delivery and administration, and an associated increase in staff satisfaction.

The use of electronic or computerized PN orders can also improve efficiency and safety and reduce errors. Maat and colleagues demonstrated a significant 16% time reduction for simple and a 60% time reduction for complex calculations related to PN prescribing in neonates when using a CPOE system with basic clinical decision support. Brown and colleagues completed a retrospective cross-sectional study evaluating the impact of an interactive computerized PN worksheet on PN-prescribing
errors. The worksheet was developed using commonly available spreadsheet software (ie, not part of an integrated CPOE system), but still required separate entry and transcription of the PN order. While use of the worksheet was associated with a reduction in the prescribing error rate, all of the errors that did occur were attributed to transcription or data entry mistakes.9

Shamliyan and colleagues completed a review of studies to examine the association between computerization of physician orders and prescribing medication orders.8 Computerized orders were associated with a 43% reduction in dosing errors, 37.5% reduction in adverse drug events, and 66% reduction in total prescribing errors in adults.8 Of the studies included in this review, 80% reported a significant reduction in total prescribing errors.8 While these data are not specific to PN therapy, they do highlight the benefits of CPOE on the medication use process and associated errors and adverse drug events.

The ISMP reported a case of a 16-year-old boy who received a PN order in which the ingredients were ordered in amounts per kg, but the PN admixture was prepared in amounts per day.21 This resulted in infusion of a hypo-osmolar PN admixture (138 mOsm/L) with very low doses of nutrients (eg, protein and dextrose both at 1 g/d rather than 1 g/kg/d) for almost an entire day before it was identified (no adverse effects were incurred by the patient). There were multiple failures across the entire medication use process in this scenario. For example, the PN order template in the CPOE system did not match the template in the pharmacy system/Automated Compounding Device (ACD). Further, there was a lack of clinical decision support and automated warnings in both the CPOE PN order template and the ACD, a lack of redundancies in the process, and multiple points of transcription. ISMP provided several safe practice recommendations21:

![Parenteral Nutrition Order Template: Adult Patient.](https://example.com/template.png)
Match prescribing and pharmacy templates
Build, test, and heed automated warnings
Heighten suspicions of errors
Carry out effective redundancies
Provide clear labeling (and the label should always match the PN order template in the PN order form/CPOE system and the ACD)
Educate and validate competency
Eliminate transcription of PN orders

Despite the potential advantages of CPOE, use of CPOE with respect to PN orders appears to be limited. A 2011 survey of PN practices noted that a CPOE system was used for PN orders in only 33% of the surveyed organizations. Most recently, Radley et al conducted a systematic review of the literature and derived a summary estimate of the effect of CPOE using a random effects meta-analytic technique. Their pooled analysis revealed that implementing CPOE was associated with a 48% (95% CI, 41%-55%) reduction in medication error rates. They further estimated that as many as 104 million medication errors could be averted annually if all hospitals fully adopted CPOE to process all medication orders. To the best of our knowledge, only one large commercial Health Information System–Electronic Medical Record/CPOE system provides even rudimentary PN calculation or decision support capability.

Question: Prescribing 3 (P3)

(P3) What improvements in the physical environment would promote safe PN ordering and use?

Recommendations

Institutions shall meet the following requirements for the physical environment as described in The United States Pharmacopeial Convention, USP General Chapter <1066>:
1. Illumination: USP <1066> recommends the following lighting levels for healthcare settings:\textsuperscript{24}
   - Computer order entry: 1000 Lux
   - Handwritten order processing: 1000 Lux
   - Sterile compounding and preparation: 1000–1500 Lux
   - Medication preparation area: 1000 Lux
   - Medication administration work area: 1000 Lux

2. Interruptions and distractions: The 2008 USP MEDMARX Data Reports noted distractions rank high (approximately 45\%) as contributing to medication errors in hospitals and health systems.\textsuperscript{25}

3. Sound and noise: The standard for sound levels for medication safety zones is set at 50 decibels A-weighted for sound (dBA), the level of conversation.\textsuperscript{24}

4. Physical design and organization of work space: The design of the workplace environment can influence the effectiveness of the prescriber to perform tasks.\textsuperscript{24} USP <1066> promotes ergonomic design of the workplace environment. Factors such as counter height, height of supplies, drawer lighting, and work clutter are noted to influence efficiency as well as safety.

5. Medication safety zones: Defined as a critical area where medications are prescribed, orders are entered into a computer or transcribed onto paper documents, and where medications are prepared, dispensed, or administered.\textsuperscript{24}

**Rationale**

The process of ordering/prescribing PN is very complex and requires an environment that promotes safety. According to the United States Pharmacopeia (USP), the work environment has been identified as one of the most common reported factors known to contribute to medication errors.\textsuperscript{24} In October 2010, The United States Pharmacopeial Convention published an official bulletin titled *Physical Environments That Promote Safe Medication Use, General Chapter <1066>*. This chapter focuses on the characteristics of the physical environment that are essential to promoting accurate medication use.\textsuperscript{24} These guidelines provide an excellent resource to promote safe prescribing for the nutrition support clinicians to incorporate into their practice.

**Question: Prescribing 4 (P4)**

(P4) How often should the PN prescription be reordered after the initial order?

1. An institution-specific or organization-specific policy should be created to dictate the duration of a PN order.

2. When reordering PN, each PN component should be reordered in its entirety, including full generic names and doses.

3. Patients with newly initiated PN should be monitored and have their orders reviewed more frequently.

4. The reordering process should be structured to require accountability for reviewing the orders, laboratory findings, and patient’s condition. Simple processes (eg, a single-step “renew order” button) that lack this accountability should not be used. The following are categories for patients and examples for their corresponding monitoring frequencies:
   a. Patients who are new to PN should be monitored daily until stable (more frequently if clinically significant metabolic abnormalities are found or patient is at risk for refeeding syndrome).
   b. Patients in an unstable clinical condition (eg, acutely ill, critically ill, recovering from critical illness, recent surgery) should be monitored daily until stable (more frequently if clinically significant abnormalities are observed).
   c. Stable patients in the hospital with no required changes in formulation for 1 week should be monitored every 2 to 7 days.
   d. Stable patients in a hospital, long-term care, or home setting with no changes in formulation for more than 1 week should be monitored every 1 to 4 weeks or longer in select clinically stable patients.

**Rationale**

There are no known studies that examine whether the duration of a PN order or the frequency with which such orders are renewed impacts outcomes or safety measures. However, the collaborative multidisciplinary care approach and application of safe practices guidelines have repeatedly proven to reduce complications, costs, and inappropriate use of PN.\textsuperscript{26} It is reasonable to assume that patients newly initiated on PN, especially those with preexisting electrolyte abnormalities or at risk for refeeding syndrome or with unstable clinical status (such as those newly critically ill or postoperative patients), will require more frequent monitoring. Similarly, patients who have been stable for some time may need less frequent monitoring. Policies regarding the frequency of PN order renewals improve monitoring practices. Protocols for ordering PN may be designed such that laboratory values must be entered or acknowledged prior to submitting the order as is common in home infusion practice. Published guidelines and literature on prescribing should be adopted and reinforced and each healthcare organization shall include clinicians with expertise in the area of nutrition support, preferably from multiple disciplines in the prescribing process.\textsuperscript{5,6}
Question: Prescribing 5 (P5)

(P5) How can education be provided to non-nutrition support specialist clinicians to improve PN prescribing and safety?

Recommendations

1. Prescribers from all disciplines, including physicians, pharmacists, nurse practitioners, physician assistants, and dietitians, should be educated on basic PN prescribing and monitoring.
2. Introductory didactic and experiential education/training about PN should be included in the core curriculum. Knowledge and skills should be evaluated for all clinicians in each discipline involved with PN as determined by the individual institution. Education and assessment materials and processes shall be developed and led by clinicians with expertise in the area of nutrition support, preferably from multiple disciplines.5,6
3. In-depth education on PN should be included as a standard component of acute care and home care pharmacy and physician residency training. This is also applicable to all pharmacists, nurses, dietitians, physicians, physician extenders, and other clinicians involved in caring for patients who receive PN.

Rationale

There are few known studies evaluating the impact of safe prescribing education programs on the outcomes of patients receiving PN. Interdisciplinary teams, applying education as part of an overall quality intervention, have been successful in reducing unnecessary PN use and decreasing errors.20 In general, participating in PN education programs has been associated with improvement in safer prescribing practices.27 Such programs are well received by students who perceive a large gap in their training in safe prescribing practices.28-30 Safe prescribing, both in general and specific to PN, should be a component of all clinical training, including the core curricula of professional programs (medical, pharmacy, advanced practice nurse prescribers, nursing, nutrition, physician assistant, etc.), residency, and specialty/fellowship programs for all who may be engaged in prescribing PN.

Topics for Further Research

1. Documentation of errors associated with PN prescribing
2. Impact of PN template standardization on PN prescribing and transcription errors
   a. Impact of listing PN ingredients in the same format using amounts per day (or amounts per kg/d), using standard units of measure (eg, mEq, mmol) on PN ordering and transcription errors, especially with transition or transfer of patient care
   b. Impact of listing PN ingredients in a standard sequence on PN order forms and whether this can improve communication and reduce PN transcription-related errors, especially with transition or transfer of patient care
3. Impact of electronic PN orders and use of clinical decision support on accuracy and safety of PN therapy
   a. Impact of electronic orders and clinical decision support vs handwritten paper PN orders on PN prescribing error occurrence
   b. Impact of CPOE interface with ACDs vs no interface vs handwritten or verbal transcription/communication on PN prescribing and transcription errors
4. Demonstration of improved patient outcomes with incorporation of appropriate monitoring parameters on the PN prescription
5. Impact of a standard commercial PN product (premixed) vs compounded PN formulation on prescribing errors
6. Demonstration of improvement in time to achieve nutrition goals and reduced length of stay with consultation from a nutrition support clinician during the PN ordering process
7. Impact of healthcare organization PN education programs, PN competency assessment, and credentialing/certification on PN ordering errors and PN safety
8. Impact of PN clinical effectiveness or quality improvement processes on PN prescribing errors

References

Parenteral Nutrition Order Review and Verification Process

**Background**

PN is a highly complicated therapy administered to patients in hospitals and alternative sites including the home and long-term care facilities. PN formulations may contain more than 40 ingredients, including amino acids, dextrose, IVFE, electrolytes, vitamins, trace elements, insulin, and other medications. PN is considered a high-alert medication because significant patient harm may occur when this therapy is used in error.1,2 A critical step in the PN process is a pharmacist’s review and verification of PN orders. Breaches in the review and verification processes have resulted in errors and patient harm.3 Healthcare organizations have the opportunity to improve the safety of PN therapy by optimizing technology for prescribing PN and transmitting PN order information as well as standardizing the PN review and verification processes.

**Question: Verification 1 (V1)**

(V1) What are the essential components or attributes for safely transmitting PN orders to pharmacists for review and verification?

**Recommendations**

1. PN should be prescribed using a CPOE system that is fully integrated with an automated compounding device (ACD).3 “Fully integrated” is described to mean that the order entered into the CPOE system is transmitted electronically to the ACD without requiring reentry of any data and any modifications to an order are electronically transmitted back to the CPOE system for physician approval and signature.
2. When PN formulations are outsourced to a third-party vendor for compounding, PN orders should be prescribed using a CPOE system and electronically transmitted to the vendor to avoid transcription errors.
3. In the absence of a fully integrated system, PN should be prescribed using a standardized order template as an
4. Verbal and telephone orders for PN should be avoided except for pharmacist to prescriber communication to modify or clarify the order.

5. PN order data should be in a standardized format, including standardized sequence of ingredients, standard units, standard formulas, and formulation options as described above in the Questions (P1–P2).

6. If transcription into the ACD is required, the output of the PN order data should be formatted to support direct entry into the ACD without requiring reordering of the ingredients, manual calculations of amounts, or unit-of-measure conversions.

7. Data should only be manually transcribed from the PN order into the ACD when absolutely necessary. Transcribed data should always be double-checked by independent processes to monitor accuracy. Multiple manual transcriptions of PN order data should be avoided.

8. PN orders should be prescribed, transmitted, and compounded when supported by properly trained personnel who regularly perform this task. This is usually during the daytime hours.

9. Vendors and application architects for CPOE systems should place priority on developing pathways for prescribing PN that support the prescriber with appropriate clinical decision support (as previously described), enforce standards of practice, and communicate directly with ACDs.

10. Application vendors and application architects for CPOE systems should collaborate with ACD manufacturers to develop fully integrated systems.

11. Application vendors and application architects for CPOE systems should collaborate with ACD manufacturers and outsourcing pharmacies to develop fully integrated systems.

Rationale

Few healthcare organizations currently use a CPOE system for prescribing PN formulations that is fully integrated with an ACD. While some healthcare organizations use a CPOE system for prescribing PN, the majority continue to use paper order forms to prescribe PN, including handwritten orders. Outsourcing pharmacies receive PN data in a variety of formats, including handwritten forms, which are commonly transmitted to the pharmacy. This may necessitate unit-of-measure conversion calculations, data manipulation, and transcription, which may result in errors. Editable electronic documents allow prescribers to complete orders and avoid the risks associated with handwritten orders. The lack of integration of the PN order with an ACD requires the manual entry of PN order data, which may lead to transcription errors. A recent survey of PN practices reported that more than half of PN orders are transcribed by a pharmacist from handwritten orders or a printed label or requisition. Two recent reports from the ISMP describe transcription errors. One was the death of a 6-week-old infant who received a dose of sodium 600 times the prescribed amount. The second report describes a PN order data entry error in which nutrients were entered into an incorrect PN template, resulting in a patient receiving a hypotonic PN formulation. Sacks et al also described a PN system in which PN order data were transcribed from a handwritten order into a hospital pharmacy computer and then reentered into the ACD, thereby increasing the risk for transcription errors. If the PN process requires transcriptions, limiting the number of times data are entered from one system to another will decrease the risk of data entry errors. PN errors associated with incorrect calculations or converting units of measure have been reported and may result in patient harm. The ISMP reported the death of a neonate who received PN that included zinc at a dose 1000 times the prescribed amount. This error was the result of a calculation error in converting mcg/100 mL to mcg/kg/d.

There are numerous CPOE vendors but few offer templates for prescribing PN that are user-friendly, allow institution-specific customization, or interface with an ACD. Although the number of orders for PN is a small percentage of the total number of medications prescribed, it is one of the most complex and complicated therapies provided by pharmacies. A CPOE system that is fully integrated with an ACD improves the safety of the PN process.

Question: Verification 2 (V2)

(V2) What improvements in the PN review and verification processes will enhance the safety of PN therapy?

Recommendations

1. Healthcare organizations shall have a written policy and procedure for pharmacists to review and verify PN orders.

2. The review and verification of PN orders should be conducted in an environment without distractions.

3. PN orders shall be reviewed by a knowledgeable and skilled pharmacist to assess that the order is clear and complete.

4. The PN order shall include the following elements:
   a. Complete patient identifiers (patient name, medical record number or other unique identifiers, patient location)
   b. Birth date and/or age
   c. Allergies and associated reactions
   d. Height and dosing weight in metric units
   e. Diagnosis/diagnoses
   f. Indication(s) for PN
   g. Administration route/vascular access device (peripheral vs central)
   h. Contact information for prescriber
i. Date and time order submitted
j. Administration date and time
k. Volume and infusion rate
l. Infusion schedule (continuous or cyclic)
m. Type of formulation (dextrose/ amino acids with separate infusion of IVFE or total nutrient admixture)

n. All PN ingredients shall be ordered as follows:
1. Ingredients ordered as amounts per day (for adult patients) or amounts per kilogram per day (for pediatric and neonatal patients) rather than in amounts per liter, percent concentration, or volume. 1 “Amount per day” refers to macronutrients in grams per day and micronutrients in mEq, mmol, mcg, or mg per day.
2. Electrolytes shall be ordered as the complete salt form rather than the individual ion.
3. The PN order should contain the full generic name for each ingredient. 1,14 Brand names should only be used when multiple products exist and/or when the brand name may assist in identifying unique properties of the specific dosage form (eg, inherent electrolytes in amino acid formulations, fatty acids in IVFE). 14
4. All abbreviations shall follow The Joint Commission standards on abbreviations. 14,15 Abbreviations on the ISMP’s list of error-prone abbreviations, symbols, and dose designations shall not be used. 16
o. A dose for each macronutrient
p. A dose for each electrolyte
q. A dose for vitamins, including multivitamins and/or individual vitamin entities. Multivitamins shall be included daily in PN formulations 1,17
r. A dose for trace elements, including multicomponents and/or individual trace element entities
s. A dose for each non-nutrient medication (eg, insulin)

5. PN orders shall undergo a clinical review to assess appropriateness and shall include the following elements:
a. Indication is consistent with published guidelines.
b. Calculated osmolality of the PN formulation is appropriate for the route of administration/vascular access device (peripheral vs central). 1
c. Each additive macronutrient, micronutrient, non-nutrient medication (eg, insulin) is evaluated to confirm that the dose is clinically appropriate for the patient’s nutrition needs, metabolic status, organ function, allergies, comitant interventions, and other indices, and to confirm that the dose is consistent with institutional practice standards.
d. The formulation is compared with the previous day’s PN formulation, if any, to assess for substantial additions, deletions, increases, or decreases in dosages of macronutrients, micronutrients, or medications (eg, insulin).
e. When laboratory data are available, updated laboratory values that have been reported since the order was submitted should be reviewed for significant changes and, if present, the appropriateness of additive dosing should be reevaluated.

6. PN orders shall undergo a formulation safety review that includes the following elements:
a. All ingredients are evaluated for compatibility with each other. Calcium-phosphate precipitation risk should be assessed according to institutional policies and procedures.
b. PN formulation is evaluated for expected stability from the time of preparation until the time that administration of the PN is complete. For example, emulsion stability of a total nutrient admixture should be evaluated.

7. Healthcare organizations shall develop policies and/or protocols to clarify PN orders when doses are outside normal ranges or potential incompatibilities may exist (eg, adjusting calcium and phosphate doses to avoid the risk of calcium-phosphate precipitation, adjusting the IVFE dose when it is not expected to be stable as a TNA [ordering IVFE separately or adjusting IVFE dosage such that the daily dose achieves minimum concentration for stability]).
8. Modifications to the prescriber’s original PN order shall be communicated to the licensed prescriber (or their designee) and documented in the patient’s medical record in a manner that is auditable.
9. All PN orders that require transcription of order data should undergo an independent double-check 4 process prior to compounding the PN formulation. The double-check shall be documented and auditable.
10. All PN orders requiring calculations or conversion of units of measure should undergo an independent double-check 4 process prior to compounding the PN formulation. All double-checks shall be documented and auditable.
11. Recommendations for pharmacy review of PN orders apply whether the pharmacist reviewing the PN order is on site or at a remote location from the prescriber. The time dedicated for the pharmacist(s) to review PN orders should be based on the average number of PN orders and the estimated time to review, clarify, and/or modify a PN order at an organization.
12. PN orders that are completed in a hospital but outsourced to a third-party pharmacy for compounding and PN orders submitted to home infusion pharmacies should undergo the same standardized pharmacy review and verification process prior to transmission to the pharmacy for compounding.

13. Institutions shall create a home PN order process that provides a safe plan for multiple days of therapy. The prescription for home PN therapy should be written in a format that specifically reflects trends in laboratory values and previous days of PN therapy. An institutional daily PN order format should not be used as a home PN prescription.

14. Pharmacies have the same responsibility of maintaining the PN orders in their records as with other medication orders.

15. The healthcare organization shall develop criteria to evaluate and identify pharmacists who are competent to review and verify PN orders.
   a. Pharmacists responsible for the review and verification of PN orders should have completed specialty residency training and/or be certified as a Board Certified Nutrition Support Pharmacist (BCNSP) by the Board of Pharmacy Specialties (BPS).
   b. In the absence of pharmacists with specialty residency training or BCNSP certification, the organization should have methods to identify and evaluate pharmacists competent to review and verify PN orders such as the certification program offered by the National Board of Nutrition Support Certification (NBNNSC) until such time that a pharmacist with specialty residency training or BCNSP certification is available.
   c. In the absence of pharmacists with specialty residency training or BCNSP certification, the organization should provide formal training programs or an opportunity to participate in formal training programs to increase knowledge and skills in nutrition support and with a goal of becoming certified in nutrition support. Training should focus on evaluating dosage of macronutrients and micronutrients as well as prescribing non-nutrient medications (eg, insulin) and their compatibilities and stabilities in PN.

16. Pharmacists who review and verify PN orders should demonstrate competency at least annually.

17. Quality improvement programs should be in place to report, track, and analyze errors associated with the PN order review and verification process.

Rationale

The review of medication orders, including PN orders, involves many steps in which the pharmacist evaluates the order for safety, efficacy, and appropriateness. These processes require knowledge of PN therapy and formulations; critical thinking and decision making by the pharmacist is crucial, and appropriate allotment of time is necessary. Before any PN formulation is compounded, the PN order is reviewed and verified. Standardizing these processes satisfies that all elements are included and the order is complete. The review and verification of PN orders includes both a clinical review and a pharmaceutical review. The verification is conducted to check that the PN order is complete and that the appropriate vascular access is in place for new patients beginning PN. Additionally, the clinical review evaluates the appropriateness of the dose of each macronutrient and micronutrient as well as non-nutrient medications in the PN formulation. A pharmaceutical review of PN orders is also conducted to determine if the prescribed components are compatible and if the PN formulation is expected to be stable.

A recent survey of PN practices reported that most institutions (60.2%) dedicate 0.6 full-time equivalent or more pharmacists to verify and review PN orders. However, 23.1% did not have any dedicated pharmacist time for these tasks. When a pharmacist is involved, most conduct both a clinical and pharmaceutical review of PN orders. The 2012 survey by the American Society of Health-System Pharmacists of pharmacy practice in hospitals reports that 11.1% of hospital pharmacies have pharmacists responsible for monitoring patients receiving PN therapy.

The complexity of PN orders necessitates special knowledge and skills to adequately review PN orders. Special training programs focusing on all aspects of the review process, especially the total daily dose of PN components, will improve the review process and heighten the pharmacist’s awareness and ability to identify errors. Identification of errors in turn requires follow-up and/or clarification with the prescriber. In the recent survey of PN practices conducted by Boullata et al, the reasons for PN order clarification included illegible orders, doses outside normal ranges, incompatible additives, and incorrect PN volume or infusion rate. Errors and patient harm have also occurred when pharmacists misinterpreted information on the PN label when patients transferred from one healthcare setting to another (eg, home to hospital). Failure to follow and be judicious with the verification and review processes have resulted in adverse events. Certification in nutrition support validates an individual’s qualifications and level of knowledge to practice in this area. BPS criteria for recognition states that the area of specialization shall be one for which specifically trained practitioners are needed to fulfill the responsibilities of the pharmacy profession in improving the health and welfare of the public, which are responsibilities that may not otherwise be fulfilled effectively. Nutrition support pharmacy practice fulfills that criteria. In one paper, staff obtained certification in nutrition support and targeted individuals with specialty certification when recruiting for new staff. This resulted in a substantial increase in knowledge and ability of pharmacists to manage the associated complexities of PN.
**Question: Verification 3 (V3)**

(V3) What are the steps healthcare organizations can take to improve the PN label and labeling system?

**Recommendations**

1. Healthcare organizations shall have a policy and procedure/protocol for standardized labeling of PN formulations.
2. Elements of the PN label include: (see Figure 3 and Figure 4)
   a. Two patient identifiers (e.g., name, medical record number, date of birth)
   b. Patient location or address
   c. Dosing weight in metric units
   d. Administration date and time
   e. Beyond-use date and time
   f. Route of administration (central vs peripheral vascular access)
   g. Prescribed volume and overfill volume
   h. Infusion rate expressed in mL/h
   i. Duration of the infusion (continuous vs cyclic)
   j. Size of in-line filter (1.2 or 0.22 micron)
   k. Complete name of all ingredients
   l. Barcode
   m. All ingredients shall be listed in the same sequence and same units of measure as PN order.
   - All PN ingredients shall be ordered in amounts per day (for adult patients) or amounts per kilogram per day (for pediatric and neonatal patients) rather than in amounts per liter, percent concentration, or volume. “Amount per day” refers to macronutrients in grams per day and micronutrients in mEq, mmol, mcg, or mg per day.
   - Electrolytes shall be ordered as the complete salt form rather than the individual ion. Each individual macronutrient and micronutrient ordered shall be listed with its corresponding dose.
   - For home or alternative site PN labels, a list of patient/caregiver additives shall be included; these additives shall be easily identified and differentiated from the other PN components. Techniques to identify patient additives include highlighting or an asterisk to identify the additives that are added just prior to administration.
3. Name of institution or pharmacy
4. Institution or pharmacy contact information, including telephone number

5. Auxiliary labels may be used to express individual electrolytes as mEq and the phosphorus content as mmol per day. The label may also include information on the amount of energy provided by each macronutrient or electrolytes intrinsic to the amino acids product.

6. If IVFEs are infused separately (vs TNA), the essential elements of the IVFE label are: (see Figure 5 and Figure 6)
   a. Two patient identifiers (name, medical record number, date of birth)
   b. Patient location or address
   c. Dosing weight
   d. Administration date and time
   e. Route of administration (central vs peripheral access)
   f. Prescribed amount of IVFE and volume required to deliver that amount
   g. Infusion rate expressed in mL/h
   h. Duration of the infusion (not longer than 12 hours)
   i. Complete name of the IVFE, even though label placed on original manufacturer container
   j. Beyond-use date and time
   k. Name of institution or pharmacy
   l. Institution or pharmacy telephone number

7. Labels for home PN formulations should be consistent with USP General Chapter <17>. (See Figure 7)
   a. Organize the prescription label in a patient-centered manner.
      - Organized in a manner that best reflects how most patients seek out and understand medical information
      - Includes only the most important patient information needed for safe and effective understanding
   b. Emphasize instructions and other information important to the patient.
      - Prominently display information that is critical for patient’s safe and effective use of therapy
      - At the top of the label, specify the patient’s name, drug name (spelling out full generic and brand name), and strength/dose. Include explicitly clear directions for use in simple language
      - Directions should follow a standard format so the patient can expect that each element will be in the same regimented order each time the medication is received
   c. Simplify language
      - Language on the label should be clear, simplified, concise, and familiar, and should be used in a standardized manner. Only common terms and sentences should be used.
● Use simplified, standardized sentences that have been developed to promote ease of understanding the instructions correctly.

d. Give explicit instructions
  ● Do not use alphabetic characters for numbers.
  ● Use standardized directions.
  ● List which PN ingredients must be added by the patient/caregiver.
  ● Ambiguous directions such as “take as directed” should be avoided unless clear and unambiguous supplemental instructions and counseling are provided.

e. Include purpose for use of PN using clear, simple terms such as “for nutrition supplementation” or “to provide nutrition”

f. Limit auxiliary information
  ● Auxiliary information should be evidence based in simple explicit language that is minimized to avoid distracting patients with nonessential information.
  ● Information should be presented in a standardized manner and critical for patient understanding and safe medication use.
  ● Use only icons for which adequate evidence suggests improved patient understanding about correct use of medication.

g. Address limited English proficiency
  ● Whenever possible, the directions for use should be provided in the patient’s preferred language, otherwise there is risk of misinterpretation of instructions with limited English proficiency, which could lead to medication errors.
  ● Whenever possible, the directions for use should also appear in English to facilitate counseling.
  ● Medication names shall be in English so that emergency personnel and other intermediaries can have quick access to the information.
  ● Translations of prescription labels should be produced using a high-quality translation process.

h. Improve readability
  ● Labels should be designed and formatted so that they are easy to read.
  ● Optimize typography using:
    ● high-contrast print
    ● simple uncondensed familiar fonts with space within letters and between letters
    ● sentence case with initial capital followed by lowercase words
    ● large font size for critical information
    ● adequate white space between lines of text
  ● white space to distinguish sections on the label such as directions for use vs pharmacy information
  ● horizontal text only
  ● never truncate or abbreviate critical information
  ● highlighting, bolding, and other typographical cues should preserve readability and should emphasize patient-centric information or information that facilitates adherence
  ● limit the number of colors used for highlighting
  ● address visual impairment

**Rationale**

PN formulations are complex mixtures with multiple ingredients. The pharmacy-generated label is a critical tool used to compare the PN ingredients and administration information against the PN order. Standardized pharmacy labels for PN formulations provide information in a clear, uniform, and organized manner, and improves the verification processes for pharmacists.\(^1\) Additionally, the label serves as a final check for those administering the PN, including nurses or patients/caregivers.\(^13\) Listing ingredients in a uniform sequence and units of measure removes the need for calculations and reduces the risk of misinterpretation. The misinterpretation of a PN label resulted in a child receiving an overdose of iron dextran and experiencing subsequent liver toxicity from iron overload.\(^23\) The lack of standardization has created confusion, especially when patients are transferred from one healthcare environment to another.\(^24\)

**Question: Verification 4 (V4)**

(V4) What processes can healthcare organizations implement to improve the safety of PN therapy during shortages of PN components?

**Recommendations**

1. Healthcare organizations (including vendors and home infusion providers) shall have a process to communicate PN component shortages and outages to prescribers and staff who participate in providing PN therapy.\(^25\)

2. Healthcare organizations shall develop and approve written PN component substitution protocols to be used in the event of a PN component shortage or outage.\(^25\)

3. Healthcare organizations shall develop and approve written protocols for PN component substitution and/or conservation strategies to be used in the event of a PN component shortage or outage.\(^25\)
**Figure 3.** Parenteral Nutrition Label Template: Adult Patient.

*Specify product name.

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Medical Record Number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Birthdate/age</th>
<th>Patient location</th>
</tr>
</thead>
</table>

Height and dosing weight: Ht: ____cm Dosing Wt: ____kg

Diagnosis(es)/Indication(s) for PN

Vascular access device/location CVC type Location

Administration date Administration time

<table>
<thead>
<tr>
<th>Macronutrients</th>
<th>Amount/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids*</td>
<td>g</td>
</tr>
<tr>
<td>Dextrose</td>
<td>g</td>
</tr>
<tr>
<td>IV Fat emulsion*</td>
<td>g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate</td>
<td>mmol of phosphate (Sodium ____mEq)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium phosphate</td>
<td>mmol of phosphate (Potassium ____mEq)</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Magnesium sulfate/chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>mEq</td>
</tr>
</tbody>
</table>

Vitamins, Trace Elements

<table>
<thead>
<tr>
<th>Multi-component Vitamins*</th>
<th>mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-component Trace Elements*</td>
<td>mL</td>
</tr>
</tbody>
</table>

Other Additives (eg, individual vitamins or trace elements, regular insulin)

<table>
<thead>
<tr>
<th>PN Instructions</th>
</tr>
</thead>
</table>

For Central (peripheral) Vein Administration Only

Total volume ____mL Overfill volume ____mL

Infusion rate ____mL/h

Start and Stop times

Cycle information

Do not use after date/time

****** Discard any unused volume after 24 hours*******

<table>
<thead>
<tr>
<th>Prescriber and Contact information</th>
</tr>
</thead>
</table>

Institution/Pharmacy Name
Institution/Pharmacy Address
Pharmacy Telephone number

---

4. Healthcare organizations have a process to communicate PN component substitution protocols and PN component conservation strategies to prescribers and staff who participate in providing PN therapy.25

5. Healthcare organizations have a process to implement PN component substitution protocols and/or PN component conservation strategies to prescribers and staff who participate in providing PN therapy.25
Figure 4. Parenteral Nutrition Label Template: Pediatric/Neonatal Patient.

- **Specify product name.**
- **Since the admixture usually contains multiple sources of sodium, potassium, chloride, acetate, and phosphorus, the amount of each electrolyte/kg provided by the PN admixture is determined by adding the amount of electrolyte provided by each salt.**

<table>
<thead>
<tr>
<th>Patient Name ______________________</th>
<th>Medical Record Number ________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthdate/age ______________________</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Patient location ____________________</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Height/Length and dosing weight: Ht/Length: ___________ cm Dosing Wt: ___________ kg</td>
<td></td>
</tr>
<tr>
<td>Diagnosis(es)/Indication(s) for PN _____________________________________________</td>
<td></td>
</tr>
<tr>
<td>Vascular access device/location CVC type __________________ Location ___________</td>
<td></td>
</tr>
<tr>
<td>Administration date ___________________ Administration Time ____________________</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macronutrients</th>
<th>Amount/kg/day$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids$^a$</td>
<td>g</td>
</tr>
<tr>
<td>Dextrose</td>
<td>g</td>
</tr>
<tr>
<td>IV Fat emulsion$^a$</td>
<td>g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate</td>
<td>mmol of phosphate (Sodium _____ mEq)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium phosphate</td>
<td>mmol of phosphate (Potassium _____ mEq)</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Magnesium sulfate/chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>mEq</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamins, Trace Elements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-component Vitamins$^a$</td>
<td>mL</td>
</tr>
<tr>
<td>Multi-component Trace Elements$^a$</td>
<td>mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Additives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysteine</td>
<td>mg/g amino acids</td>
</tr>
<tr>
<td>Others (eg, regular insulin)</td>
<td></td>
</tr>
</tbody>
</table>

**PN Instructions**

For Central (peripheral) Vein Administration Only

- Total volume __________ mL
- Overfill volume __________ mL
- Infusion rate __________ mL/h
- Start and Stop times __________________________
- Cycle information __________________________
- Do not use after date/time ______________________

***** Discard any unused volume after 24 hours********

<table>
<thead>
<tr>
<th>Prescriber and Contact information</th>
<th>________________________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Institution/Pharmacy Name</th>
<th>________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution/Pharmacy Address</td>
<td>________________________________</td>
</tr>
<tr>
<td>Pharmacy Phone Number</td>
<td>________________________________</td>
</tr>
</tbody>
</table>
PN component conservation and allocation strategies should include the A.S.P.E.N. PN product shortage considerations for multivitamins, trace elements, IVFE, amino acids, electrolyte/minerals, and cysteine. Thiamine, ascorbic acid, pyridoxine, and folic acid should be given daily. Thiamine is critical. Several deaths have resulted from cardiac failure due to thiamine deficiency when long-term PN patients did not receive vitamins for 3 to 4 weeks. Patients receiving a carbohydrate load are particularly susceptible to thiamine deficiency.17,26-31

Processes shall be in place to evaluate alternative PN components procured from compounding pharmacies, including compliance with USP General Chapter <797> Pharmaceutical Compounding-Sterile Preparations, federal laws and regulations, and state Boards of Pharmacy rules and regulations.

Processes should be in place to modify the PN order to reflect component outages and/or conservation strategies in a timely manner.

Processes should be in place to modify the PN label to reflect changes in the PN order due to component outages and/or PN component conservation strategies.

Processes should be in place to modify ACD software to reflect changes in PN components due to outages and/or conservation strategies. This includes compatibility of all ingredients and changing National Drug Code (NDC) numbers, which is mandatory for barcoding systems to function correctly. Any changes in ACD software should require two individuals to perform the validation check using a standardized process and checklist.

Quality improvement programs should be in place to track and analyze errors associated with PN applications.
Patient Name _________________________ Medical Record Number __________________
Birthdate/age ________________________
Patient location _______________________

Height/length and dosing weight: Ht/length: _____cm Dosing Wt: _____kg
Diagnosis(es)/Indication(s) for PN ____________________________________________
Vascular access device/location CVC type ___________________ Location __________

Administration date ___________________ Administration time _________________

<table>
<thead>
<tr>
<th>Infusion Volume</th>
<th>Amount/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous fat emulsion</td>
<td>mL</td>
</tr>
</tbody>
</table>

Instructions

For Central or Peripheral Vein Administration

Total volume________ mL (may contain overfill)
- syringe
- bottle

Infusion rate______ mL/h
Infuse over ______ h
Do not use after date/time_____________________

****** Discard any unused volume after 12 hours*******

Prescriber Name/Contact Information ____________________________________________
Institution/Pharmacy Name
Institution/Pharmacy Address
Pharmacy Phone Number

Figure 6. Standard Intravenous Fat Emulsions Label Template: Neonate or Pediatric Patient.

*Specify product name.

component outages and shortages. Errors associated with outages and shortages should be reported to the ISMP National Medication Errors Reporting Program.
12. Severe PN component shortage information should be reported to the FDA Drug Shortage Program, ASHP, and A.S.P.E.N.
13. During outage or shortage of PN components, clinicians shall monitor patients for deficiencies. Anticipate an increase in deficiencies with ongoing shortages. Increase awareness and assessment for signs and symptoms of electrolyte and mineral deficiencies.
14. Providers may need to seek out other sources of PN components by coordinating with other healthcare institutions or other infusion companies.

Rationale

The drug shortage crisis continues in the United States and threatens the integrity of the pharmaceutical supply chain and compromises patient care, especially patients requiring PN therapy. The number of new drug shortages has increased over the past 5 years, with the most significant being sterile injectable products.

To assess the effect of drug shortages on patient safety, the ISMP surveyed healthcare professionals. More than 1800 healthcare professionals responded and reported 1000 medication errors or adverse patient events due to a drug shortage. Of those who responded, 35% reported their institution had experienced a near miss during the past year due to a drug shortage; 25% reported an actual error, and 20% reported an adverse patient outcome. Another drug shortage survey was conducted by Premier Healthcare Alliance. Over 300 pharmacy experts from hospitals and other healthcare sites participated. Shortages that may have resulted in a medication safety issue or error in patient care were reported as having been experienced by 89% of respondents.

To understand the impact of PN product shortages on patient safety, each step of the PN process should be considered. The steps of the PN process include procurement, management, prescribing, order review, compounding and dispensing,
administration, monitoring, and patient outcomes. In a recent survey, 16.4% of respondents reported that patient outcome was directly affected by PN-related product shortages, including nutrient deficits, increased length of stay, and increased morbidity and mortality.\(^8\) Managing PN product shortages includes activities such as developing and revising policies and procedures for rationing or restricting PN products, use of alternative products, prescribing systems, and changes in compounding and dispensing as the result of shortages.

PN product shortages may be so critical that prescribers may elect not to provide PN therapy because there are no products to prevent or treat complications. Outsourcing pharmacies

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**Figure 7.** Standard Home Parenteral Nutrition Label Template: Adult Patient (as an Example).

\(^a\)Specify product name.

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Patient Home Address</th>
<th>Birthdate/Age</th>
<th>Height and dosing weight: Ht: ____ cm Dosing Wt: _____ kg</th>
<th>Vascular access device/location CVC type</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration Date/Time/Indication</th>
<th>Infuse 1 bag each day for nutrition.</th>
<th>Infuse at _____ mL per hour over ____ hours</th>
<th>Start at _______(time)</th>
<th>Stop at _________(time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macronutrients</th>
<th>Amount/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids(^a)</td>
<td>g</td>
</tr>
<tr>
<td>Dextrose</td>
<td>g</td>
</tr>
<tr>
<td>IV fat emulsion(^a)</td>
<td>g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate</td>
<td>mmol of phosphate (Sodium ____ mEq)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium phosphate</td>
<td>mmol of phosphate (Potassium ____ mEq )</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>mEq</td>
</tr>
<tr>
<td>Magnesium sulfate/chloride</td>
<td>mEq</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>mEq</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamins, trace elements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-component Trace Elements</td>
<td>mL</td>
</tr>
<tr>
<td>Add prior to administration</td>
<td></td>
</tr>
<tr>
<td>Multi-component vitamins(^a)</td>
<td>mL to be added immediately prior to administration</td>
</tr>
<tr>
<td>Other Additives</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>______ Units to be added immediately prior to administration</td>
</tr>
<tr>
<td>Medications</td>
<td>______ Medication specific units (mcg, mg, g)</td>
</tr>
</tbody>
</table>

Specify if requires adding immediately prior to administration.

<table>
<thead>
<tr>
<th>Total Volume</th>
<th>mL</th>
<th>Overfill volume</th>
<th>mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do not use after: Date __________ Time __________

Prescriber’s name/phone number

Institution/Pharmacy Name
Institution/Pharmacy Address
Pharmacy Phone Number
may dictate to customers PN product conservation strategies. Although this is severe, the PN product shortages have resulted in prescribing suboptimal therapy due to shortages or rationing of products. The prescribing step is affected as prescribers find it difficult to keep up with shortages, alternative products, rationing, restrictions, and so on. Furthermore, the prescribing process is constantly changing, and prescribers may use workarounds to circumvent safety checks. Lastly, an increase in the number of prescribing errors has been associated with shortages.31

Many of the same safety concerns have been identified in the PN order review step. Pharmacists who perform this step have difficulty staying current with shortages, alternative products, and rationing. There has been an increase in the number of PN orders that require clarification or those with prescribing errors.

The compounding and dispensing steps are associated with numerous patient safety issues resulting from PN product shortages. As with other aspects of the PN process, those responsible for compounding and dispensing find it difficult and stressful trying to keep up with the many shortages. During a shortage, alternative products that are unfamiliar or are similar in appearance to other products may be substituted. This may lead to errors. Furthermore, PN may be compounded using alternative products such as calcium chloride or magnesium chloride, for which there are insufficient stability and compatibility data or known unfavorable differences. Frequent changes in PN products or the size of the source containers necessitate a change in the configuration of ACD, increasing the potential for error. Some products cannot be configured for the ACD, requiring a manual addition to a PN formulation. Frequent changes in products, alternative products, ordering process, and ACD configuration may result in PN orders and PN bag labels that do not match. This creates significant concerns for those responsible for the administration of the PN admixture.

The PN product shortages affect the administration of PN whether administered by a nurse, patient, or caregiver. Just like others involved in the PN process, it is difficult and stressful to keep current with the shortages. As noted above, the PN order and PN bag labels may not match as the result of changes in the compounding process. With some shortages, patients may require supplemental electrolyte or mineral infusions when the alternative product cannot be added to the PN formulation due to stability or compatibility concerns. Increasing the number of times the patient’s intravascular device is accessed may increase the risk of catheter-related bloodstream infections.29 A recent study of PN practices reported the consequences of PN product shortages. Of the pharmacists responding, more than two-thirds reported that valuable time is consumed in developing contingencies. Additionally, 70.3% of respondents indicated that shortages interfere with the ability to meet patients’ micronutrient needs, and almost half reported that shortages interfere with ability to meet macronutrient needs.8

The lack of a PN component increases the risk of a deficiency of that nutrient or complications. Shortages have been associated with patient harm. Anemia and leukopenia due to copper deficiency has been reported in an adult patient receiving PN without trace elements for 4 months.35 Clinicians must have a heightened awareness of potential deficiencies and monitor for the deficiencies or associated complications.

The shortages pose safety risks throughout the entire PN process, from procurement to patient outcomes. Providing PN therapy during product shortages requires vigilance and continuous assessment of the entire PN process to optimize patient care quality and avoid patient harm.

Topics for Future Research

1. Demonstration of decrease in PN errors when CPOE systems are fully integrated with ACDs.
2. Demonstration of decrease in PN errors with elimination of handwritten paper PN orders and use of editable electronic orders or CPOE systems for prescribing PN.
3. Documentation of PN errors associated with PN verification process.
4. Documentation of PN errors associated with the clinical and pharmaceutical reviews of PN orders.
5. Documentation of PN errors associated with transcription of PN data from the order to an ACD.
6. Impact of PN order standardization on PN data transcription errors.
7. Demonstration of PN error reduction with implementation of standardized review and verification of PN orders.
8. Demonstration of a reduction in PN errors with implementation of a standardized checklist for verification and review of PN orders.
9. Impact of a fully integrated electronic system for prescribing PN and data into an ACD.
a. Demonstration of medication error reduction
b. Demonstration of improved patient safety
c. Demonstration of decreased costs
10. Documentation of PN errors associated with PN order calculations.
11. Documentation of PN errors associated with misinterpretation of PN bag labeling.
12. Demonstration of PN error reduction with standardized PN labeling.
13. Development and implementation of a standardized home PN label that is consistent with the A.S.P.E.N. Safe Practices for PN and USP General Chapter <17>.
14. Evaluation of patient understanding and satisfaction with PN labeling that is consistent with the A.S.P.E.N. Safe Practices for PN and USP General Chapter <17>.
15. Demonstration of reduction in PN errors when PN orders are reviewed by a pharmacist with specialty residency training and/or BCNSP certification.
17. Demonstration of PN error reduction with PN formal training programs for pharmacists and pharmacy technicians.
18. Compatibility of PN components, including macronutrients, micronutrients, and non-nutrient medications.
19. Determination of maximum osmolarity of PN formulations for administration via peripheral veins.
20. Impact of PN product shortages on patient outcomes.

References
Compounding

Background

Recent PN errors caused by a knowledge deficit, lack of training, insufficient competency, and poor proficiency with ACDs are areas of significant concern. Additionally, a lack of competency-based educational curriculum in schools of pharmacy or pharmacy technician training programs may contribute to PN errors. Very few suitable studies exist that characterize the formalized training of pharmacy students or technicians in the preparation of sterile products and admixtures. Available data suggest that when pharmacy students are formally taught aseptic technique skills with direct observation and assessment of parenteral compounding procedures, microbial contamination rates related to medium-risk level compounding (eg, PN compounding) decreased significantly from baseline toward the end of the 16-week course.1 Several recommendations pertaining to the knowledge and competency of staff involved in the preparation of compounded sterile products were developed at the recent ISMP Sterile Preparation Compounding Safety Summit.2 Surveys of pharmacists at the beginning of postgraduate training programs demonstrated that first-year pharmacy residents reported minimal experience (median = 2) on a scale from 1 to 5 (5, most experience and 1, no experience) with PN evaluations and IV admixtures. This suggests that there are educational deficits in current pharmacist training related to areas important for institutional or homecare pharmacy practice.3 Observational data from practicing hospital pharmacists and pharmacy technicians revealed that compounding error rates were 37% when PN formulations were manually compounded and 22% when prepared with an ACD. Errors included touch contamination, incorrect calculations performed by technicians, and bypassing the built-in safety check systems on ACDs.4

Question: Compounding 1–2 (C1–C2)

(C1) What compounding errors have been caused by deficits in knowledge, lack of training, competency, and proficiency?
(C2) What compounding errors have been caused by a lack of standardized educational curriculum in schools of pharmacy or pharmacy technician programs?

Recommendations

1. Schools of pharmacy in the United States shall develop curricula that address proper aseptic technique and USP Chapter <797> for making compounded sterile preparations (CSPs).
2. Pharmacy technicians shall be certified by the Pharmacy Technician Certification Board if they are involved in the making of CSPs, including PN.
3. Healthcare organizations shall provide a broad orientation with an in-depth training program focusing on CSPs for all staff members supervising or participating in the preparation process. An ongoing competency assessment program shall be included in the training as well.
4. Healthcare organizations shall require annual competency evaluations of pharmacists and pharmacy technicians involved in preparation of CSPs. This should include:
   a. Calculations
   b. Compounding base solutions
   c. Preparing dilutions or aliquots
   d. Aseptic technique manipulations
   e. Using technology (ie, ACD) for preparation
   f. Anticipating incompatibilities (calcium, phosphate)
5. Organizations should develop a strategic plan for implementation of automation and technology for the sterile products service.
6. Pharmacists and pharmacy technicians shall be proficient in the proper use of technology (ie, ACD) when used for preparation of CSPs.
7. State Boards of Pharmacy should create a specific license and licensing requirements for infusion pharmacies and compounding pharmacies.
8. State Boards of Pharmacy should provide an in-depth training program focusing on CSPs for all State Board inspectors. An ongoing competency assessment program should be included in the training as well.

Rationale

The lack of standardized training emphasizing foundational concepts behind sterile compounding and aseptic technique is startling in today’s professional programs educating both pharmacists and pharmacy technicians. Over the past 5 years, numerous reports of serious morbidity and mortality have appeared in the lay press due to a lack of training in aseptic technique with preparation of sterile products. The most recent tragic events have surrounded a rare outbreak of fungal meningitis that was traced to several lots of the injectable glucocorticoid methylprednisolone acetate compounded by the New England Compounding Center. Although these sterile injections were intended for back and joint pain, a lack of sterile compounding competency has sickened hundreds of patients and killed dozens.5 Even more relevant are the 9 deaths that occurred in Alabama during the preparation of amino acids under high-risk conditions and an error in sterile compounding technique. It is incumbent on pharmacists to check that all people involved in the oversight and preparation of CSPs obtain appropriate training and be evaluated on a regular basis through a competency assessment. Pharmacists would receive education in the physicochemical principles of pharmacy and practice experiences as part of a pharmacy school curriculum. Technicians would receive education in the operations of ACD hardware and software with varied practice experiences as part of the curriculum. Board certification for those involved in CSPs could guarantee a basic minimum requirement in lieu of
formalized training as part of a curriculum. The criteria required for nutrition support pharmacy board certification would suggest that these individuals are better prepared to allow fewer errors, although no data are available to support this contention. Anecdotal data would suggest that pharmacists and pharmacy technicians with specific education and many hours of hands-on experience are in the best position to be involved with PN compounding. In the workplace, pharmacists and technicians should participate in a comprehensive orientation and training program with an ongoing competency assessment plan. This plan would evaluate all aspects of sterile compounding from calculations to the proper use of technology.

**Question: Compounding 3 (C3)**

(C3) How can organizations avoid PN errors by implementing soft and hard limits on an ACD?

**Recommendations**

1. Organizations shall implement specific computerized soft limits and hard (catastrophic) limits for PN ingredients based upon pharmacists’ review that are consistent with the needs of their patient population.
2. Access to the ACD database is limited to select individuals qualified to manage and maintain this activity and all changes are traceable. Pharmacists and technicians shall be educated on interpretation and limitations of calcium-phosphate compatibility curves in the software.
3. Weight-based warning limits for doses shall be developed by clinicians with the assistance of the vendors. As an alternative, organizations may develop and use their own weight-based warning limits.
4. Only pharmacists shall be allowed to override alerts. An independent double-check process should be completed by another pharmacy staff member, ideally another pharmacist.
5. Healthcare organizations should check that all unresolved ACD alerts encountered during the PN order entry process should be presented to the person reviewing the order entry so they can also view and respond to the alerts.
6. Healthcare organizations shall reinforce the importance of reacting to the ACD alerts and documenting all interventions.
7. Healthcare organizations should review available reports detailing the frequency of overrides as well as the frequency of overrides for specific PN components.

**Rationale**

Limits can be placed on the doses of each PN component to optimize safety within the compounding process. These limits can be automated within the PN order-prescribing, reviewing, and/or compounding process. The term “hard limits” refers to alerts that indicate that a component is outside a determined safe range and shall not be exceeded; these are also referred to as “catastrophic” given patient outcomes if exceeded. “Soft limits” refer to alerts that indicate an unusual dose that requires further evaluation. Once addressed, any alert that is overridden or any dosing that is revised will require documentation of the rationale. Compared with manual methods, the software application available with ACDs should lead to improved compounding accuracy, enforcement of proper compounding sequence, and a reduction in opportunities for human touch contamination. However, preparing PN admixtures with an ACD is not an error-free process. Error rates in compounding complex preparations such as PN admixtures have been reported to be 22% when automated in part and 37% when manually prepared. Organizations may improve the safety of using PN compounding systems by requiring that all doses being compounded pass through an order entry/clinical decision support system and by ensuring that those systems’ clinical decision support features are properly enabled and configured. Transmission of PN order data from an order-calculating software package into a compounding device should be avoided. In a recent survey on PN use, Boullata et al found that dose limit warnings were active in only two-thirds of organizations that used ACDs for preparing PN formulations. ISMP Medication Safety Alerts from 2007 and 2011 described incidents in which adverse outcomes resulted, in part, from the absence of dose limit warnings. In both instances, infants received lethal doses of a micronutrient (zinc in one case, sodium in the other) when a manual order entry error was either not detected by the existing dose limits or dose limit alerts were not active. After reviewing the incidents, ISMP made a number of safe practice recommendations. Among these was the recommendation to install, test, and maximize automated dose-limit warnings in the pharmacy computer system and the ACD order entry system, particularly for high-alert medications such as PN and its ingredients. Further, ISMP recommends that each organization develop weight-based dosing limits applicable to their patient populations, as ACD vendor-established “catastrophic” limits may still allow entry of a potentially fatal dose into the software without issuing a warning.

The ASHP guidelines on the safe use of ACDs for the preparation of PN admixtures state that the pharmacy department should develop a monitoring and surveillance plan that promotes safe and efficacious use of the device at all times. This plan should include a review of dose-limit alerts and overrides, utilizing the reporting capabilities of the ACD or pharmacy computer system.

DeBoer and Maddox described a review of smart pump data after implementation throughout the Sanford USD Medical Center. Three to six months of smart pump data were collected for each unit and an analysis of edit variance detail and override variance detail was performed. After the initial review
was completed, data were analyzed for medications included in the ISMP high-alert medication list. Work practices were evaluated and revised with the goal of encouraging fewer edits and overrides. In a similar fashion, data from the ACD or pharmacy computer system should be regularly reviewed in the assessment of trends and other long-term measures of performance.

**Question: Compounding 4 (C4)**

(C4) What role does United States Pharmacopeia (USP) Chapter <797> play in preventing PN errors?

**Recommendations**

1. Healthcare organizations shall comply with USP Chapter <797> standards.12
2. Outsourcing should be considered as an alternative to in-house compounding when the healthcare organization does not possess the technological resources or staffing to prepare PN admixtures according to USP Chapter <797>. The decision to outsource should require that the pharmacy outsourcing PN production exercise due diligence to monitor that the outsourcer also operates within USP <797> guidelines.
3. Standardized, commercially available PN products may be viable options to manually compounded sterile PN products when compliance with USP Chapter <797> and accepted guidelines from patient safety organizations is not feasible.
4. Healthcare organizations shall have policies and procedures that address using multichamber, standardized, commercial PN products within their formulary.
5. Healthcare organizations shall have well-defined policies and procedures that guide the preparation of PN admixtures.
6. Healthcare organizations must identify standardized workflow processes that include quality control, process change control, and documentation practices. These standardized operating procedures should encompass the entire compounding process from order entry to verification of the final labeled product.
7. Healthcare organizations should develop a strategic plan to include technology/automation for sterile compounding and consider using IV workflow software.2
8. When an ACD is used to prepare PN admixtures, policies and procedures shall be developed that address performance requirements and responsibilities, control of the ACD in daily operations, safety and efficacy features, quality assurance monitoring and documentation, storage and inventory, education and training, and device variability and maintenance.
9. Privileges to make changes in the ACD database shall be restricted to a limited number of pharmacy staff who are well trained in both the theory and the mechanics of this process.2
10. Customized order entry templates created by organizations should have a documented standard review process by qualified staff person that includes review and testing of the clinical decision support that is expected to alert the pharmacist to significant warnings. The use of a checklist or sign-off sheet shall be required and two staff members, including at least one pharmacist, shall sign off on or validate the template.2
11. The additive sequence in compounding shall be optimized and validated as a safe and efficacious method. Manufacturers of ACDs shall provide an additive sequence that promotes the safety of the compounding device. This compounding sequence should be reviewed with the manufacturer of the PN products used by the organization.13
12. The use of a checklist or signoff sheet shall be required when adding new products, including new and alternative generics, changes in vial size or concentration, and when making other modifications to the ACD database (eg, changes in privileges, changes in data requirements). Two staff members shall be required to sign off on or validate changes. (This process would not apply to inputting a new lot number for a product already in the database.)2
13. Barcode verification shall be used to verify product identity during ACD setup and replacement of ingredients.2
14. An independent double-check process for the initial daily ACD setup shall be performed by two staff members using a printed checklist. Verbal affirmation should take place to validate placement of all additives and base solutions, including name, concentration, and container size.2 When the vendor of the compounding system describes a validated system for proper setup, that system should be followed.
15. Tubing set(s) shall be traced from the source container to the port where it is attached during the initial daily ACD setup and with each change in the source container.2
16. If multiple containers of a single additive are used during the preparation of a single CSP, all empty containers shall be presented to the pharmacist and verified as part of the final check process prior to dispensing the final CSP.2
17. When an ACD is used, it should deliver all ingredients. Manual compounding should only be used:
   a. If the volume of a PN component to be mixed is less than the ACD can accurately deliver.
   b. If there is an interaction between a PN component and a component of the ACD (eg, insulin and tubing).
   c. If there is a chemical interaction between PN components that cannot be mitigated by sequencing the addition of ingredients.
   d. During a shortage of a specific PN component, manual compounding can be a consideration as part of conservation efforts.
Verification of manual additives should include inspection of the actual vials and syringes that contain the additives. Proxy methods of verification (e.g., syringe pullback) shall not be used. If the manual method is being used, the process should be standardized to promote safety and efficacy. The use of a checklist or sign-off sheet shall be incorporated into the manual process. PN orders should be prescribed, transmitted, and compounded when supported by properly trained personnel who regularly perform this task. This is usually observed.

At least three verification processes should occur in the pharmacy: (1) after initial order entry of PN, (2) before manually injecting additives into the PN, and (3) once the PN has been compounded. In-process or end-product testing requires that the PN preparation be held pending results. It may be better to fully automate and validate the entire PN compounding process to prevent errors from being made in the first place.

Organizations should develop a drug conservation policy that addresses the handling and disposition of PN components (while maintaining their integrity and sterility) that may be in short supply due to market conditions, as these shortages can affect workflow conditions.

The physical environment in which PN compounding takes place should be assessed in terms of lighting, interruptions and distractions, sound and noise, ergonomics, and medication safety zone. USP General Chapter <1066> describes optimal physical environment standards that promote safe medication use throughout the medication-use process. Any deficiencies should be addressed following organizational chain of command.

Once a standardized process for compounding PN has been implemented, organizations should review and revise the process on an annual basis along with a review of personnel compounding behavior.

Operation of the compounding process must be routinely observed for procedural compliance and corrective action must be taken immediately if noncompliance is observed.

Rationale

An ASHP national survey of pharmacy practice in hospital settings published in 2012 found that overall, 65% of hospital pharmacy departments reported having a United States Pharmacopeia (USP) Chapter <797> compliant cleanroom. Having a USP Chapter <797> compliant cleanroom differed significantly by hospital size, with more than 87.5% of the largest hospitals (600 or more staffed beds) having a compliant cleanroom, compared with 48.1% of hospital pharmacy departments in hospitals with fewer than 50 beds. Commercially available PN multichamber bags were used by 36% of hospitals as the predominant form of PN formulation. ACDs were used by 20.4% of hospitals, followed by gravity methods (17.4%) and outsourcing compounding activities (14.6%); 11.6% of hospitals did not prepare PN formulations. The method of preparing PN differed significantly by hospital size. Larger hospitals most commonly used ACDs or outsourced preparations. Hospitals with fewer than 50 staffed beds most commonly used commercially available dextrose/amino acid formulations or TNA did not prepare any PN admixtures or used gravity methods to prepare PN.

Organizations should refer to a number of available guidelines and articles regarding standardization of the PN compounding process (see Table 2). Organizations compounding PN admixtures must have well-defined policies and procedures to guide each step of preparation and shall comply with standards set forth in USP Chapter <797>. Compounding PN “as usual” is no longer acceptable if it does not comply fully with USP Chapter <797>. Error rates in compounding complex preparations such as PN admixtures have been reported to be 22% when automated in part and 37% when manually prepared. Error rates of 24% in PN preparation were identified in a prospective observational study.

Compounding errors that result in an unexpected patient event occur in 30% of hospitals. The USP chapter that describes the compounding of sterile preparations provides minimum practice and quality standards based on current scientific information and best sterile compounding practices. Organizations that are unable to comply with USP Chapter <797> and accepted guidelines from patient safety organizations should consider alternative compounding options such as outsourcing or standardized commercially available PN products.

Policies that require prescribers to order PN daily before a specified deadline should be established and enforced to maximize the safety with which these admixtures are prepared and dispensed. Pharmacy staff should be aware of all patients who are receiving PN and check if orders have not been received by the established deadline. PN ingredients considered to be very small volumes that staff manually prepare, check, and inject require verification, including inspection of the vials and syringes containing such additives. Verification of manual additives should include inspection of the actual vials and syringes that contain the additives. Proxy methods of verification such as the syringe pull-back method of verification should not be used in the preparation of PN and other high-alert CSPs and shall not be used without the presence of the actual original source containers (medication and diluent).
Table 2. Documents Discussing the Standardization of the Parenteral Nutrition Preparation Process.

<table>
<thead>
<tr>
<th>Source Title</th>
<th>Publisher</th>
<th>Publication Year</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Chapter &lt;797&gt; – “The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from the following: (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles (see ‘official’ and ‘article’ in the General Notices and Requirements) or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) incorrect types and qualities of ingredients in Compounded Sterile Preparations (CSPs).”</td>
<td>USP</td>
<td>2006</td>
<td>12</td>
</tr>
<tr>
<td>ISMP Sterile Preparation Compounding Safety Summit Proceedings</td>
<td>ISMP</td>
<td>2013</td>
<td>2</td>
</tr>
<tr>
<td>ASHP guidelines on the safe use of automated-compounding devices for the preparation of parenteral nutrition admixtures.</td>
<td>ASHP</td>
<td>2000</td>
<td>10</td>
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</tbody>
</table>


Independent double-checks should be incorporated into the compounding process. At least three verification processes should occur in the pharmacy: (1) after initial order entry of PN, (2) before manually injecting additives into the PN, and (3) once the PN has been compounded. Each step in the verification process should require a pharmacist to compare the actual prescriber’s order to the printed labels, and the printed labels to the additives and final product, as appropriate. Verification of manual additives should include inspection of the actual vials and syringes that contain the additives. The final verification of the compounded PN should include a comprehensive review of the PN order, the label on the product and the compounding work label, and a visual inspection of the CSP. Quality control checks and verification of replacement components on the compounder either manually or via barcoding should also be required, as should an independent double-check of any calculations.9

PN multichamber bags, which are designed to reduce the risk for instability or precipitation, are available. These multichamber bags separate components of the PN formulation with a bar or seal until just prior to activation and administration. The contents of the chambers should be mixed and any additives introduced by pharmacy staff prior to dispensing the formulation. However, if these products are used in home care, patients and/or caregivers shall be provided with thorough training regarding the procedure for properly mixing the product before use. In addition, the containers should be accompanied by auxiliary labels alerting users to the need to mix the product prior to administration.

Organizations should review and revise the PN compounding process on an annual basis. A number of analytical methods have been applied to another high-risk complex compounding process, such as the preparation of chemotherapy. Bonan et al describe a multidisciplinary team’s application of the Hazard Analysis and Critical Control Points method to preparation of anticancer drugs.20 The team identified 11 critical points. Monitoring, control measures, and corrective actions were identified for each risk. Over a 10-month period, 16,647 chemotherapy preparations were compounded with 1157 nonconformities for the 11 critical control points. These included 693 compounding sheet errors and 131 analytical nonconformities. Aboumatar et al reported the outcomes of application of Lean Sigma solutions to the chemotherapy preparation process.21 Once mistake-proofing interventions were introduced via workspace redesign, process redesign, and developing standard operating procedures for pharmacy staff, reported medication errors reaching patients causing an increase in patient monitoring decreased and the number of reported near misses increased. These improvements would be welcomed in the PN use process.

**Topics for Further Research**

1. The impact of the educational level and training of sterile compounding personnel on PN compounding error rates.
2. The impact of State Boards of Pharmacy inspections on PN compounding error rates.
3. Impact of the sequence for adding macronutrients, micronutrients, and non-nutrient medications on PN stability and compounding error rates.
4. Impact of multichamber PN admixtures (commercially available vs customized compounded) on stability, including risk of precipitation.
5. The impact of standardized, commercial PN products vs customized compounded PN admixtures on infections, stability, and preparation errors.

References

Parenteral Nutrition Administration

Background
Because PN administration errors occur at the point of patient contact, mistakes in this phase of the medication delivery process are less likely than other types of PN errors to be intercepted and more likely to cause harm. In addition, the broad range of healthcare settings in which PN administration takes place—from critical care to home care—raises the potential for disparities to exist in the technology, equipment, and knowledge and skills of the nursing staff and caregivers responsible for PN administration. Although once uncommon, PN is administered with increasing frequency in long-term care and skilled nursing facilities. Regardless of the setting or the number of patients receiving the therapy in a given facility, the classification of PN as a high-alert medication requires healthcare organizations to develop evidence-based policies and procedures designed to promote safe PN administration and to validate the competence of those responsible for delivering this complex form of IV therapy.

Question: Administration 1 (A1)
(A1) What system-based measures can organizations implement to enhance the safety of PN administration?

Recommendations
1. Written policies and procedures shall be developed to standardize nursing practices for the administration of PN throughout the organization.
2. Education and competency assessment shall be provided to newly hired nurses and patients or caregivers who are responsible for PN administration.
3. Healthcare organizations should conduct ongoing validation of competency in PN administration based on changes in practice related to PN administration, results of medication error monitoring, and/or the
vulnerability of the patient population (eg, high acuity patients, including neonates and the critically ill).

4. Healthcare organizations that provide nursing services related to home infusion shall establish mechanisms for periodic reassessment of knowledge and techniques used by patient or caregivers for home PN.

5. Interdisciplinary quality improvement programs shall incorporate analysis of medication errors associated with PN administration and knowledge of errors that occur in other institutions.

6. Safeguards shall be implemented to address specific problem areas as indicated by analysis of PN administration errors.

7. An interdisciplinary process should be employed for selecting and evaluating equipment and technological aids, such as smart pumps and barcoding to reduce errors in PN administration.

8. Healthcare organizations shall develop policies and procedures that address extravasation of PN formulations.

9. Acute care facilities should establish a policy that prohibits the use of a PN formulation prepared for administration at home or in subacute or long-term care facilities.

10. Protocols for safe operation of infusion pumps shall stipulate rules regarding alarm silencing, modification, and disabling.

11. Healthcare organizations should purchase infusion pumps with capacity to reduce errors due to incorrect programming. Whenever possible, infusion pumps should be standardized throughout the organization.

Rationale

Data pertaining to the incidence of errors related to PN administration are scarce. A recent survey revealed that 44% of organizations do not track PN-related medication errors and do not know where in the process errors may be occurring.1 The literature does provide some insight into the scope of the problem. In particular, the frequency with which case reports of PN-related errors involve neonatal and pediatric patients suggests that this population may be most vulnerable to PN administration errors.2

One prospective observational study of errors associated with PN found that 35% of PN-related errors occurred during the administration process.3 In a similar audit of 18,588 PN days in a tertiary pediatric hospital, administration-related errors accounted for 30% of all PN errors.4 In addition, data gathered over a 5-year period from a national medication error-reporting program revealed 266 errors associated with IVFE in neonatal intensive care units, 93.2% of which occurred in the administration phase.5,6 Another report of quality improvement data from a single 39-bed unit caring for neonates to young adults indicated that in one 6-month period, PN and IVFE errors accounted for 25% of all medication errors.7

Standardized Procedures and Competency Validation. Failure to follow established procedures plays a prominent role in PN administration errors.2 While human factors frequently contribute to PN errors, organizational efforts to strengthen the safety of PN administration must extend beyond a focus on individual performance and center on identifying system-based approaches to reduce errors.8,9 Fundamental to this process is the development and articulation of nursing policies and procedures for PN administration that standardize nursing practices based on published clinical guidelines.2,5,10 These policies and procedures shall be reviewed and revised on a regular basis. Table 3 provides an outline of essential components of nursing procedures for safe PN administration.

Healthcare organizations, regardless of setting (acute care to home care), shall conduct ongoing education of nurses and patients or caregivers and establish mechanisms to validate competence in PN administration. At a minimum, competency validation should occur in the following circumstances: as part of orientation for newly hired nurses, when a change in protocol or procedure takes place, with the introduction of new equipment or technology, and when quality improvement monitoring or other data sources reveal a gap in skills or knowledge related to PN administration.11 Home infusion nursing care providers shall establish processes for periodic reassessment of knowledge and techniques used by patients or caregivers in the delivery of PN in the home.12 Studies of educational initiatives aimed at reducing intravenous medication errors have not consistently produced the desired impact on error rates.13 The optimal strategy (simulation, case scenarios, observation, etc) for providing continuing education aimed at reducing medication errors remains unclear, emphasizing the importance of using a variety of educational strategies and maintaining vigilance in evaluating their effectiveness.

Policies and procedures related to PN administration should address management of extravasations of PN formulations into perivascular or subcutaneous tissues.14-18 Although most often associated with peripheral vein infusions, PN extravasation can occur with all types of vascular access devices (VADs).11,17 A number of factors influence the extent of tissue damage, including pH, osmolality, electrolyte content, and duration of tissue exposure.17 No controlled trials are available for the management of PN extravasations, but consensus-based recommendations include stopping the infusion, aspiration of residual fluid, elevation of the limb, and application of cold therapy.11,17 Treatment with hyaluronidase has also been described for extravasations of PN and hypertonic dextrose.17,19 Education for nursing staff and nutrition support clinicians should include ongoing assessment of the vascular access site and appropriate interventions in the event of an extravasation.

Organizations must also develop policies pertaining to the administration of PN formulations brought in from home or from another facility. The inability to verify the stability and sterility of the formulation—as required by The Joint Commission standards—raises serious safety concerns.20 The lack of medical and pharmacy review can potentially lead to
the infusion of compromised PN formulations or prescriptions that are not appropriate for the patient’s current clinical status. Accordingly, 75% of organizations currently prohibit the use of preparations brought from home.¹

Role of technology. Technological advances hold much promise for improving the safety of PN administration. Yet only 33% of healthcare organizations report using CPOE for PN orders, while 20% employ barcode medication administration (BCMA).¹ Little evidence is available regarding the impact of these technological aids in reducing errors in the PN administration process. CPOE appears to offer benefits in preventing errors in the prescription and transmission phases rather than those associated with PN administration.²¹⁻²³ BCMA technology serves as an aid in verifying patient identity, but errors can occur when clinicians bypass the safety features of the system. Complex admixtures such as PN present challenges with BMCA systems because current technology cannot validate that the label on a formulation containing multiple ingredients accurately reflects the contents of the PN container.

Infusion pumps have long been seen as a requirement for PN administration.²,¹¹ Yet despite their widespread use as a safety measure, pump-related mishaps stand out as a frequent factor in PN administration errors.⁴,⁶ At a minimum, infusion pumps should feature accurate volume (rate control), anti–free flow controls, and alarms for sensing air and pressure changes in the administration tubing, as well as dose error reduction software.¹¹,²⁴ Protocols for safe operation of infusion pumps shall stipulate rules regarding alarm silencing, modification, and disabling.

Table 3. Essential Components of Nursing Policies and Procedures for PN Administration.

| A. Role responsibilities, delegation considerations |
| B. Required equipment |
| C. Verification procedures |
  1. Confirmation of patient identity according to organizational policy |
  2. Use of PN formulas prepared in another institution |
  3. Checking PN label against the order including formulation components, route, and rate of delivery, expiration date |
  4. Inspection of formulation to detect defects or visual changes |
  5. Verification of appropriate vascular access prior to initiating PN infusion |
    - Tip location: newly inserted lines and those in place on admission |
    - Safeguards to avoid tubing misconnections—trace tubing to the body before making the connection |
    - Confirm patency |
D. Administration |
  1. Policy regarding verification of pump settings |
  2. Observation of formulation integrity during infusion |
  3. Importance of maintaining PN infusions at the prescribed rate—avoid interruptions for routine care or adjustments for infusions that are off schedule |
  4. Guidelines for medication administration for patients receiving PN |
    - Policies for co-infusing IVFE or other medications with PN |
    - Policies prohibiting additions to PN formulations on clinical units |
  5. Recognizing a compromised PN formulation |
  6. Significance of clogged filters |
E. Infection control measures |
  1. VAD dressing care procedures, aseptic management of catheter hub |
  2. Frequency of tubing and filter change |
  3. Hang time |
  4. Minimizing manipulations |
    - Dedicated line, lumen |
    - Blood-drawing practices |
F. Monitoring |
  1. Appropriate blood glucose monitoring based on clinical condition and infusion schedule (cycled vs continuous infusion) |
  2. Laboratory monitoring |
  3. Evaluating response to therapy |
  4. Recognition and intervention for extravasation |
G. Complications and troubleshooting |
H. Termination of therapy |
I. Patient education |
J. Documentation
In recent years, infusion pumps equipped with software designed to detect potential errors (“smart pumps”) have become available, although conflicting information exists regarding the use of these devices. A recent gap analysis that specifically addressed current PN practices found that smart pumps are available in 29% of responding facilities. On the other hand, a survey of hospital-based pharmacies reported a usage rate of 77% for these devices. Smart pumps provide a safeguard against programming errors and capture data that can support quality improvement programs. When used properly, smart pumps reduce the potential for error, but this pump technology is not foolproof. If a smart pump drug library is bypassed or is used incorrectly or if the infusion rate and volume are manually entered, a dose error can occur. One case study, for example, reported an incident in which a PN infusion was administered at 10 times the prescribed rate for 2 hours when a soft limit alert was bypassed. The advantages of smart pumps can be offset by the complexity of programming the pumps and maintaining a current drug library. To have a meaningful impact on patient safety, smart pumps must be integrated with BCMA and CPOE systems as well as hospital and pharmacy information systems. A comprehensive organizational commitment to the technology of smart pumps is essential to the successful deployment in clinical areas. Organizations should purchase infusion pumps with capacity to reduce errors due to incorrect programming. Whenever possible, infusion pumps should be standardized throughout the organization to promote user familiarity with the operation of the device.

Quality improvement. A critical step in efforts to improve the safety of PN is the implementation of quality improvement programs designed to track and analyze errors associated with PN administration. However, only 39.9% of organizations report having an ongoing quality improvement process for PN. Proactive and reactive methodologies, failure mode effects analysis, root cause analysis, and the Plan-Do-Study-Act (PDSA) model should all serve as the framework for identifying high occurrence or high impact errors, closing practice gaps, and engendering continuous process improvement. Multifaceted interdisciplinary approaches must foster a culture of safety, clarify problem areas, involve key stakeholders, test change strategies, and maintain channels of communication. These key concepts are most effective in bringing about and sustaining behavior change.

As noted earlier, smart pumps can serve as a valuable source of quality improvement data that allows organizations to track practices related to PN administration and identify interventions that address safety breaches. However, without a reliable wireless network, data retrieval can be labor intensive.

**Question: Administration 2 (A2)**

(A2) What strategies can prevent errors in the verification phase of PN administration?

**Recommendations**

1. The verification process of PN administration should be presented in a bundle format, which uses a set of evidence-based interventions for a defined patient population or care setting.
2. Nurses, caregivers, and patients shall visually inspect the integrity of the PN container and formulation before spiking the container.
3. The PN label shall be verified against the original prescriber order. No verbal orders shall be accepted.
   a. Check the patient identifiers, product name, route of administration (central vs peripheral), designated initiation time, infusion rate, and beyond-use date and time.
   b. Match all components listed on the label of the formulation to the PN order.
4. A printed copy of the PN prescription shall be provided to home PN consumers initially and with each formulation change to allow this verification step.
5. Patient identity shall be confirmed using two identifiers according to organizational policy.
6. The administration tubing shall be traced to the point of origin in the body at the initiation of the infusion and at all handoffs.
7. An independent double-check process and verification of infusion pump settings should be performed by a second clinician before beginning the PN infusion and documented in the medical record.

**Rationale**

PN administration errors often stem from failure to adhere to the verification steps of PN administration, which parallel the “five rights” of medication safety that all nurses learn: right patient, right drug, right dose, right route, and right time. Policies and procedures for PN administration should avoid broad directives to “check the label” but instead provide clear procedural guidance for each step in the verification process. This verification process should be presented in a bundle format, which uses a set of evidence-based interventions for a defined patient population or care setting. As with other bundles used in healthcare, all components of the verification process must be implemented together to achieve improvements in care.

Adherence to the “five rights” is not sufficient in preventing medication errors. Although human factors frequently contribute to errors, healthcare organizations have a responsibility to create an infrastructure that supports safe practice and reduces the potential for error. This includes educating staff about the proper use and effectiveness of double-checks and creating procedures for reporting errors, near misses, and barriers to safe practice in a nonpunitive environment.
enteral formula, human breast milk, and cardioplegia solutions, posing the risk for wrong-product or wrong-route errors. Practices related to the delivery and storage of these items can mitigate the likelihood of such errors, but the importance of the verification process as the final step before the point of patient contact cannot be overstated.

Nursing education for PN administration shall include information about managing of potentially compromised or unstable PN formulations. This includes inspection of PN formulations prior to initiating the infusion and at regular intervals during the infusion. Any formulation that displays evidence of precipitants, particulate matter, or an unstable formulation shall be returned to the pharmacy for further investigation.

Other examples of lapses in the verification process include PN administration to the wrong patient by the wrong route—infusing a central formulation via peripheral vein or through an incorrect tubing connection—or at the wrong rate. The nurse or caregiver should be provided access to the complete original PN order to facilitate verification of all elements of the order (ie, patient identifiers, nutrient dosing, infusion rate, etc.).

Mistakes involving incorrect infusion rates are among the most common errors reported. Often, these errors are related to mistakes in programming a single infusion pump, but the risk for rate errors appears to increase when IVFE and dextrose/amino acid components are administered as separate infusions. Errors involving incorrect infusion rates pose the greatest risk for patient harm due to the potential for causing life-threatening metabolic disturbances such as hyperglycemia or fat overload syndrome.

**Tubing misconnections.** Inadvertent catheter tubing misconnections have been recognized as a serious problem in healthcare. Although the administration of enteral feeding through intravenous devices has been associated with the most serious injuries, accidental connections between intravenous tubing and other systems that rely on Luer connectors have been reported, including epidural, intracranial, intrathecal, and tracheal tubing systems. Because tubing used to administer PN must be changed every 24 hours, the potential for a misconnection occurs at more frequent intervals than with conventional intravenous fluids. Clear labeling on PN containers, tubing, and pump channels can reduce the risk of inadvertent misconnections. However, the single most important risk reduction strategy is to trace all tubing back to its origin before connecting devices or infusions and to recheck connections and trace all patient tubes and catheters to their sources at the start of each shift and upon the patient’s arrival to a new setting or unit as part of the hand-off process.

**Independent double-checks.** Reports of PN-related errors often recommend implementation of independent double-checks at critical phases of PN administration, such as order verification or programming the infusion rate into the pump. To be effective, an independent double-check must involve two clinicians separately checking the infusion settings in accordance with the prescriber’s order, alone and apart from each other, then comparing results. Although double-checks serve as a valuable safety mechanism if performed correctly, the process may require up to 20 minutes of additional nursing time. Other barriers include a lack of clarity regarding the procedure for double-checking and a culture that does not fully support peer review. Furthermore, excessive use of double-checks can dilute the effectiveness of this safety mechanism. Independent double-checks should not be implemented to address problems that could be corrected through system redesign. Nevertheless, organizations that have identified errors in conjunction with a specific component of the PN verification process, such as order verification, patient identification, or pump programming, should implement double-checks strategically to avert potentially harmful errors. For optimal effectiveness, independent double-checks should be used in conjunction with other error reduction strategies and system changes aimed at reducing the risk of medication errors. The use of computer-generated checklists with PN infusion instructions has been suggested as a way to guide verification procedures without increasing workload demands, but this approach requires further study.

**Question: Administration 3 (A3)**

What practices maintain patient safety during the infusion of PN?

**Recommendations**

1. PN shall be administered by or under the supervision of trained, competent personnel.
2. Organizations shall establish evidence-based policies to guide the selection, insertion, care, and maintenance of VADs used to administer PN.
3. PN protocols shall include measures to reduce contamination through manipulation of the catheter hub.
4. VADs used for PN administration should not be used to obtain blood samples for laboratory tests unless no peripheral access is available.
5. PN infusions shall be infused through a filter appropriate for the type of formulation.
6. An occluded filter shall never be removed in response to occlusion alarms, thus allowing the unfiltered formulation to continue to infuse.
7. Administration tubing should be attached to PN containers immediately prior to use.
8. Administration tubing and filters shall be changed with each new PN container (every 24 hours for TNAs and dextrose/amino acid formulations; 12 hours for IVFE infused separately).
9. For prolonged infusions of IVFE (20–24 hours), the daily dose should be divided into 2 parts, with a new container and tubing every 12 hours.

10. Policies regarding PN multichamber bags should be developed using a multidisciplinary approach.

11. The PN infusion shall be maintained at the prescribed rate:
   a. Correct pump settings shall be verified at regular intervals and at each hand-off.
   b. The PN infusion rate shall not be adjusted if the infusion is off schedule.
   c. The rate of PN shall not be increased in response to changes in fluid needs; additional hydration should be provided as a separate infusion.
   d. The PN should not be interrupted for routine care or patient transport for diagnostic studies.
   e. Organizations shall develop policies regarding PN infusion and appropriate metabolic monitoring during surgery.

12. The timing and frequency for blood glucose monitoring shall be based on clinical status and performed in a manner appropriate for the PN infusion schedule (cycled vs continuous).

13. Caution shall be used when administering subcutaneous insulin coverage prior to a scheduled interruption of the PN infusion.

14. In acute care acute settings (including long-term acute care), no additions should be made to PN formulations outside the compounding pharmacy; in home settings, additions to PN formulations should be limited in number and be made as close as possible to initiating the infusion.

15. In long-term care facilities and in home care, education should be provided and caregiver competency regarding proper technique for the addition of prescribed additives to PN formulations should be verified.

16. Co-infusion of medications through PN lines shall require a review of compatibility and stability data by a pharmacist.

17. PN should be discontinued prior to transfer to another facility.

18. The administration of PN and the patient’s tolerance shall be documented in the medical record.

**Rationale**

Nursing care during PN infusion centers on administering the infusion as prescribed, preventing complications, monitoring metabolic stability, assessing progress toward therapeutic goals, and documenting patient response to therapy. This process includes safe and effective management of all medical devices and equipment used in the delivery of PN, safe administration of medications in conjunction with PN therapy, and optimal care of vascular access devices.

**Medical devices and equipment. Vascular access:** Reliable vascular access is essential for safe and effective delivery of PN. A wide array of VADs are available, but some are better suited to PN delivery than others. Factors that influence the selection of a VAD for PN include the patient’s medical condition, need for concomitant intravenous medication(s), the anticipated duration of PN therapy, and the setting in which PN is administered. In all care settings, the patient’s views should also play a role in the decision-making process for VAD selection.

Despite their essential role in PN administration, VADs are a leading cause of serious adverse complications related to PN therapy, in particular, central line–associated bloodstream infection (CLABSI). PN is an independent risk factor for CLABSI, requiring organizations to be especially vigilant in establishing policies to guide the selection, insertion, and care of these devices. In recent years, widespread implementation of a bundle of evidence-based guidelines for insertion and maintenance of VADs has achieved substantial reductions in the CLABSI rates. In addition to addressing VAD insertion and site care, PN protocols shall also include measures aimed at reducing contamination that occurs through manipulation of the catheter hub. Some organizations maintain policies requiring a dedicated line or lumen for PN administration, although studies have not yielded consistent results regarding the efficacy of this practice.

Many organizational protocols for care of VADs discourage blood sampling from central lines as part of an overall effort to reduce manipulation and subsequent contamination of the catheter hub. For similar reasons, The Joint Commission has highlighted the use of VADs for blood sampling as a “practice to avoid.” One recent study of home PN recipients found an increased risk for CLABSI in patients who routinely had blood drawn from a VAD, leading these authors to conclude that PN catheters should not be used for obtaining blood samples unless no peripheral access is available. The elevated risk for CLABSI that is associated with PN administration warrants a multifaceted approach to CLABSI prevention that targets all pathways for VAD infection.

The use of VADs for blood withdrawal not only increases the risk for microbial contamination of the line and hub, but samples drawn incorrectly from a VAD during PN infusion can also lead to spurious laboratory values. Binkley et al first drew attention to the danger of this phenomenon in a report of a 10-month quality assurance study. More recently, a year-long prospective cohort study in an academic medical center found 63 incidents of spurious blood work in 34 PN recipients. In both cases, investigators recount incidents of patient harm—typically hypoglycemia or hypokalemia—that resulted from unnecessary medical intervention for falsely elevated laboratory values.

**Filters:** In-line filters are required for PN administration to reduce the potential for patient harm due to particulates, microprecipitates, microorganisms, and air emboli. These devices
should be placed as close to the patient as possible on the administration system. A 0.22-micron filter is recommended for a dextrose/amino acids formulation; a 1.2-micron filter is used for a TNA formulation. Because nurses must deal with the problem of pump alarms at the point of care, nursing competencies for PN administration shall include appropriate actions and troubleshooting in response to high-pressure alarms or an occluded filter. This education shall emphasize that a filter that becomes occluded during PN administration should raise suspicions that the incorrect filter size has been used or that a precipitate or particulate is present in the formulation. When an occluded filter triggers pump alarms, the PN infusion shall be stopped. Before resuming PN, a pharmacist should review the PN formulation to determine if incompatibility issues are the cause of the problem and to identify actions to prevent further occurrences.

Filters are manufactured for single patient use and should be changed according to the manufacturer’s guidelines. The typical maximum use interval for PN filters is 24 hours. Due to the potential for contamination and subsequent release of endotoxin, filters should not be primed with PN fluid in advance—in the compounding pharmacy, for example. Instead, the filter should be filled with fluid immediately before initiating the infusion.

**Administration tubing and containers:** PN formulations should be provided in a single daily bag, with the exception of IVFE that is administered as a separate infusion. The PN admixture should be kept refrigerated and protected from light exposure between the times it is dispensed until just before infusion. Exposure of PN formulations to ambient light generates peroxides and other degradation products, potentially contributing to oxidant stress. Concern regarding the clinical impact of this phenomenon has led to recommendations that PN be shielded from light, especially for neonates. However, studies have failed to demonstrate clear clinical benefits of shielding PN formulations from light. Partial light protection offers no clinical benefit. To reduce PN degradation, the container and tubing must be protected from light at all points from compounding through administration. Further research is required to determine if complete photoprotection of PN formulations can lead to improved clinical outcomes.

The administration tubing should be attached to the PN container, using sterile technique, immediately prior to initiating the infusion. Although there may be workflow advantages to spiking the container and priming tubing in advance, no studies have examined the safety of this practice. Infection control guidelines for non-nutrition intravenous fluids stipulate that the infusion begin within 1 hour of inserting the tubing spike into the container. The issue of whether the risk of contamination could be reduced by spiking the PN container in an ISO Class 5 environment or higher remains unknown.

IVFE administered separately shall be appropriately labeled and administered in keeping with the organization’s policies and procedures for minimum/maximum hang times. PN containers and administration sets shall be free of the plasticizer di-2-ethylhexyl phthalate (DEHP) to prevent DEHP contamination of TNA formulations and IVFE that are infused separately. Guidelines for the frequency of tubing changes for PN formulations often make a distinction between admixtures that contain IVFE (every 24 hours) and those that contain only dextrose and amino acids (no more frequently than 96 hours). However, these recommendations overlook the potential for contamination of the filter on all types of PN formulations. Therefore, administration sets and filters should be changed with each new PN container. For continuous infusions, this interval will typically be every 24 hours; cycled PN will require tubing and filter changes based on the hours of the infusion. Administration sets used for IVFE infused separately shall also be changed with each new infusion (hang time 12 hours). In cases in which a prolonged IVFE infusion is desirable to promote tolerance, the daily fat emulsion dose should be divided into 2 parts, with a new container and tubing used every 12 hours.

Multichamber PN bags are available, which are designed to reduce the risk for instability or precipitation. These multichamber bags separate components of the PN formulation with a bar or seal until just prior to administration. The contents of the chambers should be mixed and additives introduced by pharmacy staff prior to dispensing the formulation. However, if these products are used in home care, patients and/or caregivers shall be provided with thorough training regarding the procedure for properly mixing the product before use. In addition, the containers should be accompanied by auxiliary labels alerting users to the need to mix the product prior to administration.

**Infusion practices.** PN infusions should be administered according to the prescribed rate via an infusion pump. Nurses shall verify the correct rate when the PN infusion is initiated, at regular intervals during the infusion, and at hand-offs. Scheduled changes in the prescribed administration rate should be based on patient tolerance and metabolic stability. In acute care settings, PN is commonly infused continuously over 24 hours. However, a schedule in which the PN is cycled to infuse over 10 to 14 hours (based on patient tolerance) can offer physiologic and psychological benefits to patients in selected circumstances. The conversion from a continuous to a cycled administration period typically takes place by reducing the infusion time by 4 to 6 hours each day until the infusion time has been compressed to the target duration. However, one recent study suggests that cycling PN to 12 hours can be accomplished in one step. A report documenting a high incidence of adverse events associated with PN cycling underscores the importance of close patient monitoring during the transition to cycled PN. At each stage, the healthcare team must assess tolerance of the cyclic infusion before advancing to the next step.

Hyperglycemia, edema, or symptoms of fluid intolerance signal the need for a more cautious approach to cyclic infusion. Adult patients tolerate abrupt discontinuation of PN without
experiencing rebound hypoglycemia. However, a 30- to 60-minute taper-down period is customarily used with ambulatory PN infusion pumps that perform this function automatically. On the other hand, pediatric patients younger than 2 or 3 years old are prone to developing hypoglycemia with abrupt discontinuation of PN and therefore require more gradual taper-down procedures in conjunction with cycling. During the transition to a cycled PN regimen, on-cycle and off-cycle glucose monitoring should take place daily. Once patient tolerance to cycled PN is established, less frequent glucose monitoring may be acceptable, especially in stable home PN patients.

When transitioning to cyclic PN, dosing regimens for insulin should be tailored to avoid abnormal fluctuations in blood glucose levels. In patients for whom PN is the sole source of nutrition, giving subcutaneous correctional dose insulin in the final phase of the cycle could lead to hypoglycemia when the PN infusion is discontinued. On the other hand, when PN formulations contain large doses of insulin, patients may require intermediate or long-acting insulin to prevent hyperglycemia after the PN stops.

Unscheduled interruptions in the infusion should be avoided because they may contribute to metabolic disturbances and suboptimal nutrient delivery. PN administration should not be interrupted for medication administration. PN should be discontinued prior to discharge or transport to another facility. As noted earlier, a taper-down period is a gradual reduction in the PN rate. Adult patients do not require a taper; however, a taper period for pediatric patients receiving PN prevents rebound hypoglycemia.

The risks of metabolic complications, particularly those related to glycemic control, have raised questions regarding the safety of continuing PN during operative procedures. However, no studies have adequately examined this issue. One survey of pediatric anesthesiologists revealed a high degree of variability in the clinical management of blood glucose levels in patients receiving PN during anesthesia. As with other areas of PN administration, healthcare organizations should develop clear and consistent policies that address intraoperative PN infusion. When the PN infusion is continued during surgery, the prescribed infusion rate should be maintained, with close monitoring of blood glucose levels and insulin administration as needed to maintain glycemic control. The use of PN infusions for fluid resuscitation shall be avoided.

Medication administration. Historically, PN formulations were viewed as convenient vehicles for delivery of medications such as heparin, insulin, and histamine (H2) receptor antagonists. However, a better understanding of factors that impact the stability of PN formulations and the potential for drug-nutrient interactions warrants a more conservative approach to medication administration with PN formulations. The mixture of medications in PN preparations is being addressed more specifically in A.S.P.E.N.’s forthcoming parenteral nutrition clinical guidelines, which are to be published in the near future. Incompatibility reactions range from discoloration, degradation of nutrients or medication, and formation of precipitates, to loss of emulsion integrity in TNA formulations. The greatest risk for incompatibility exists with medications that are added directly to the PN formulation due to the prolonged time of contact between the medication and PN components with direct admixtures. Standardized commercial PN products that require further additives prior to patient administration should be prepared in the pharmacy under aseptic conditions. Therefore, in acute care settings, policies shall be implemented that prohibit the addition of medication outside the compounding pharmacy. However, in home care settings, stability considerations often require that medication, such as multivitamin preparations or insulin, be added to PN formulations prior to initiating the infusion. In this case, the addition of medication should take place as close to the beginning of the infusion as possible. Patient and caregiver training in the proper technique for adding medication to PN formulations shall be documented. The additions should be made as close to the beginning of the infusion as possible to reduce the potential for harm should touch contamination occur during this process.

As noted earlier, the optimal way to administer PN is through an IV line (one lumen of a multilumen VAD) reserved solely for that purpose. However, maintaining a dedicated line for PN administration may be impractical or impossible in patients who receive multiple IV medications or have limited vascular access. Pharmacists must conduct a comprehensive review of stability and compatibility data from the literature and manufacturer of intravenous nutrients before a medication is administered in a PN formulation.

As with all high-alert medications, PN should be administered as a primary infusion. Co-infusion of medication through the same tubing used for PN should also be avoided if possible. Compatibility information should be derived for PN that closely matches the formulation in question. Medication administration policies should explicitly detail safe practices with regard to medication administration in conjunction with PN.

Documentation. Organizational policies and procedures shall define documentation practices related to PN administration in accordance with legal and regulatory requirements. This should include, but is not limited to, initiation and discontinuing times of the infusion, rate, route of administration, results of capillary glucose monitoring and laboratory tests, condition of the VAD, patient’s response to therapy, progress toward therapeutic goals, and patient education provided.

Topics for Further Research

1. Identification of the optimal use of independent clinician double-checks in critical aspects of the PN administration process.
2. Identification of educational strategies that are most effective in developing and validating competence in PN administration procedures.
3. Demonstration of PN error reduction with routine assessment of competence in PN administration procedures.
4. Identification of environmental and human factors that contribute to PN administration errors.
5. Identification of strategies to mitigate the risk of PN administration errors.
7. Impact on infection rates and accuracy of laboratory tests with the use of vascular access devices to obtain blood samples for laboratory tests.
8. Clarification of the appropriate use of filters with IVFE administration.

References


**Question**

1. Does education of prescribers improve PN ordering?

2. What is the maximum safe osmolarity of a PN admixture intended for peripheral vein administration?

3. What are the appropriate calcium intake and the calcium-phosphate ratios for optimal neonatal bone mineralization in PN therapy?

4. What are the clinical advantages/disadvantages of premixed PN formulations compared with traditional/customized PN formulations?

5. What are the clinical/cost advantages/disadvantages of 2-in-1 compared with 3-in-1 PN admixtures?

6. What macronutrient dosing limits provide for the most stable 3-in-1 admixtures?

7. What are the most appropriate recommendations for maximizing calcium (gluconate) and (Na- or K-) phosphate compatibility in PN admixtures?

8. What micronutrient contamination is present from parenteral stock solutions currently used to compound PN admixtures?

9. Should the PN admixture be used as a vehicle for non-nutrient medication delivery?

10. Should heparin be included in the PN admixture to reduce the risk of central vein thrombosis?

11. What data support a methodology for the repackaging of intravenous fat emulsion (IVFE) into smaller patient-specific volumes?

12. What beyond-use date should be used for a. IVFE dispensed for separate infusion in the original container, and b. repackaged intravenous fat emulsion (IVFE)?
Conclusion

PN serves as an important therapeutic modality used in adults, children, and infants for a variety of indications. The appropriate use of this complex therapy aims to maximize clinical benefit while minimizing the potential risks for adverse events. Complications can occur as a result of the therapy, as well as the result of the PN formulation process. These consensus recommendations are based on practices generally accepted to minimize errors with PN therapy and categorized in the areas of PN prescribing, order review and verification, compounding, and administration. These recommendations should be used in conjunction with other A.S.P.E.N. publications, and researchers should consider studying the questions brought forth in this document.

Author Note

Safe Practices for Compounding of Parenteral Nutrition
Michael R. Cohen
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What is This?
Safe Practices for Compounding of Parenteral Nutrition

Michael R. Cohen, RPh, MS, ScD, FASHP

Abstract
Safe practices for sterile compounding are essential to preventing errors, particularly with parenteral nutrition (PN). This article reports several areas of errors in PN processes and provides recommendations for error prevention. (JPEN J Parenter Enteral Nutr. 2012;36:14S-19S)

Keywords
electrolytes/acid-base; outcomes research/quality; parenteral formulas/compounding; parenteral nutrition

Errors during pharmacy preparation of parenteral products and admixtures have been reported to the Institute for Safe Medication Practices (ISMP) over the years. As early as the 1990s, observational studies on the accuracy of preparing small- and large-volume injectables, chemotherapy solutions, and parenteral nutrition (PN) showed a mean error rate of 9%, meaning almost 1 in 10 preparations were prepared incorrectly and then dispensed.1 Error rates for complex solutions such as PN were especially high—37% for manual preparation and 22% for preparations that were partly automated. More recently, a 2009 State of Pharmacy Compounding Survey showed that 30% of hospitals have experienced a patient event involving a compounding error in the past 5 years.2

Recently, several high-profile intravenous (IV) admixture error cases have received media attention, several of which specifically related to PN compounding, engendering a decision by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) to conduct a PN safety summit. In preparation for the meeting, a review of past error reports submitted to the ISMP National Medication Errors Reporting Program (ISMP MERP) was conducted to describe some of the commonly reported contributing factors. Although the causes of these errors are numerous and varied, examples of pharmacy PN preparation errors follow.

Wrong Dextrose Concentration
A serious issue in the early years of PN compounding was confusion between 5% dextrose large-volume parenteral containers and 50% or 70% dextrose, mainly due to similar packaging. In some cases, mix-ups were also reported between amino acid and dextrose solutions. In one case, a patient erroneously received 70% dextrose instead of 10% amino acids. In another, a fold in the bag made a 7 look like a 1, contributing to a mix-up between 70% and 10% dextrose. The error was discovered the following morning when the 70% dextrose bag was noticed on the pharmacy’s automated IV compounder. Fortunately, practitioner recognition of these problems, as well as labeling and packaging improvements by large-volume parenteral solution manufacturers, has helped to reduce these types of incidents. In addition, incorporation of refractometer testing and a final check of the actual total bag weight compared with a calculated expected weight has also resulted in fewer such reports to the ISMP.

Other PN Product Mix-ups
Mix-ups between 250-mL containers of 5% dextrose and potassium chloride concentrate have occurred, suggesting that potassium additive solutions must be carefully stored and controlled while in use. The ISMP frequently receives reports about mix-ups between small-volume and large-volume parenteral products such as heparin sodium and magnesium sulfate, potassium phosphate and magnesium sulfate, and many others. Best practice dictates that every organization have at least 1 individual who regularly reviews ISMP reports to identify potential problems at their location. Often problems can be avoided by working with group purchasing organizations to modify purchasing contracts when, for example, 2 different products are known to look nearly identical to one another.

Whenever possible, have a pharmacist pull the necessary products prior to compounding of the preparation and place them in a bin to give to technicians. Technicians should then verify the products and, if they do not match what is expected, ask questions before preparation. Optimally, either bar coding should be used with an automated compounder, or an independent check of ingredients should be made by the pharmacist before product is prepared if bar coding is not used. Ensure that
preparations are discarded if there are any doubts, even if minor, about the compounding and storage of the preparation.

**Catheter Misconnections**

Luer connector systems, common to many healthcare catheters, tubes, administration sets, extension sets, and syringes, have been at the heart of many catheter/tubing misconnections. At the center of one of the most commonly reported problems is the fact that some manufactured enteral catheters still have end connectors that only accept parenteral administration sets and syringes. Then, even if a liquid medication is prepared in an oral syringe, the medication must be transferred to a parenteral syringe for administration via this type of enteral tube connector, risking the accidental administration of the drug via a parenteral line. In addition, lines have been jury-rigged to make an incompatible fitting work.

Breast milk has been given intravenously to neonates and bladder irrigation solutions of amphotericin B (yellow in color) have been confused with PN solutions with vitamins and given intravenously. Likewise, PN solutions with vitamins have been administered via Foley catheters. Also, IV administration sets have been spiked into enteral nutrition containers, resulting in enteral nutrition solutions administered intravenously.

Catheter/tubing misconnections are a serious problem in healthcare. The International Organization for Standardization (ISO) has been working with the Association for the Advancement for Medical Instrumentation (AAMI) on a standard (ISO/IEC/FDIS 80369-1, “Small-bore connectors for liquids and gases in healthcare applications”) that will result in making various healthcare catheter fittings and associated tubing sets or syringes incompatible with one another.

It is important for organizations to perform a risk assessment to identify the various types of catheters and fittings now in use, identify the possibility for misconnections, assess the potential severity of misconnections, and address process changes that need to be made. For example, 2 easy-to-implement risk reduction strategies common to most types of catheter/tubing misconnections include (1) always tracing the port and tubing back to its insertion site to verify the correct access/route of administration and (2) never attempting to force or jury-rig a connection that does not fit easily and securely into an access port.

**Issues Related to Drug Shortages**

A national shortage of common electrolyte solutions, vitamins, and trace elements in certain strengths and sizes has forced many pharmacists to replace their standard injectable solutions with a different product. These products, sizes, or concentrations that have been in short supply include concentrated sodium chloride 14.6% and 23.4%; potassium phosphate injection; potassium acetate injection; zinc chloride injection; selenium, calcium gluconate injection; and calcium chloride injection. As a result, it has become critically important to follow a formal verification process, not only for purchasing alternative products and making inventory adjustments but also for ensuring that necessary changes are made within computer software that drives various medication use systems, such as IV compounders and computer order entry systems, smart pumps, and any other affected technology.

At issue with automated IV compounders is that the National Drug Code (NDC) number in the compounding software tags the specific concentration of the listed electrolyte. However, there is no interface for communication with the pharmacy order entry system where NDC numbers are updated when product changes occur. Thus, if the compounding software is not changed manually to reflect the new product and NDC number, bar-coding systems will not properly detect a difference between the software and the product being scanned for use with the compounder.

Pharmacists must ensure that a workable, standard process exists and is well understood by practitioners for making these adjustments with all due care. Omitting this important step could easily result in a serious error. Require that 2 individuals perform the validation check of these database modifications using a standardized process and checklist. Start by having 1 staff member make the change to the database and prepare the checklist. Then have this same individual read the changes aloud from the checklist while a pharmacy supervisor or second designated individual confirms the changes. The checklist should be countersigned by a pharmacy supervisor after the change has been validated. This checklist would not be required for the addition of lot numbers and expiration dates, as is required as part of the routine production process.

In addition, shortages have sometimes led to compounding of sterile preparations by sterile IV compounding pharmacies when manufacturers have been unable to supply. However, a lack of governmental oversight for USP chapter <797> compliance in many states, as well as confusion over which of these pharmacies are regulated by the U.S. Food and Drug Administration (FDA) as manufacturers and thus required to follow current good manufacturing processes, has led to a dearth of information about which of these compounding pharmacies provide an appropriate level of safety for the preparations they provide. In some cases, quality control compliance has been compromised, resulting in inadvertent contamination of solutions. For example, the Alabama Department of Public Health (ADPH) reported an ongoing investigation of an outbreak of *Serratia marcescens* bacteremia associated with contaminated PN bags in 6 Alabama hospitals. An investigation by the ADPH and the Centers for Disease Control and Prevention (CDC) led to the discovery that because of a shortage of certain commercial amino acid solutions, a compounding pharmacy prepared batches of solutions from nonsterile powders of amino acids. Sterilization of the solutions ultimately failed, resulting in cases of *S marcescens* bacteremia in 19 patients, 9 of which resulted in fatalities.
The ISMP has called upon the FDA to work collaboratively with the state boards of pharmacy to provide them with the necessary support and training to survey compounding pharmacies for compliance with USP Chapter <797>. Furthermore, we believe compounding pharmacies that distribute sizable quantities (to be defined by the FDA) of preparations, as well as those operating interstate, should be registered with the FDA and subject to periodic inspections. We also encourage the FDA to move forward with plans to publish guidance on Good Pharmacy Compounding Practices for Sterile Drug Products and the Outsourcer Pharmacy Operations Compliance Policy Guide (www.ismp.org/search?k=ucm079647) to clearly articulate requirements for registration with the FDA, periodic inspections, support available to the state boards of pharmacy, and expectations regarding the state boards’ role in regulating compounding pharmacies.

As a result of drug shortages, sometimes pharmacists advise a switch to oral forms of drugs. This was the case during a recent shortage of parenteral multiple vitamins. In such cases, patient medication administration records should be monitored to ensure that patients are actually receiving the oral replacement. Sometimes, because of taste or gastrointestinal (GI) issues, or because oral medications may not be considered as important as injectables, doses are left unadministered.

**Failure to Incorporate IV Compounder Catastrophic Limits**

Not all automated compounders have the inherent software capability to establish catastrophic limits to ensure an inadvertent catastrophic amount of electrolyte is not delivered. Even when limits can be set, it may still be possible for an entry to be made without a hard stop if the PN order is entered into a non-PN patient-type template that the user can create without dose limits. Another possibility is if an adult application of the software was purposely used to enter the neonatal PN where the limits set are far too high for the infant. Patient safety dictates that pharmacies preparing PN solutions with electrolytes should install, test, and maximize automated dose limit warnings in the pharmacy computer system and automated compounders, particularly for high-alert medications such as PN and its products.

**Insulin Mix-ups With Heparin**

Several incidents have been reported where mix-ups between heparin and insulin were at issue. In one case, a bag of PN contained insulin instead of heparin. A blood glucose level of 17 mg/dL was reported for a premature baby in the neonatal intensive care unit (NICU), 6 hours after a PN infusion had been started. Despite multiple bolus doses of dextrose and an infusion of dextrose 20% in sodium chloride 0.45%, the hypoglycemia did not completely resolve until discontinuing the PN. Although the infant survived, the baby’s long-term well-being had not been assessed at the time of the report. Insulin has been accidentally added to infant PN in other cases known to the ISMP, each with fatal outcomes. In addition, a 1991 ISMP article describes cases of severe hypoglycemia after one pharmacist added 200 units of insulin instead of heparin to PN and another added 1000 units of insulin instead of heparin to PN. Also, in other cases in our database, 2 patients, neither of whom was diabetic, died after being injected with insulin instead of heparin during a vascular catheter flush procedure. And in yet still other reports, a nurse flushed a patient’s central line catheter with insulin instead of heparin, and another erroneously transcribed a verbal order to resume an insulin drip as “resume heparin drip.”

The most common factors associated with these mix-ups seem to be (1) similar packaging of insulin and heparin in 10-mL vials and placement of insulin and heparin vials, both typically used each shift/day, next to each other on a counter or under a pharmacy IV admixture hood and (2) mental slips leading to confusion between heparin and insulin, especially because both drugs are dosed in units. Some implanted catheters are flushed with 100 units per mL of heparin, and insulin is commonly available in a concentration of 100 units per mL. Perhaps the risk of a mental slip is growing, as insulin infusions are more commonly used in recent years.

To prevent confusion between heparin and insulin vials during drug preparation, do not keep insulin and heparin vials alongside one another on top of counters or drug carts or under the laminar flow IV admixture hood in the pharmacy. Many organizations do not allow insulin near the location where PN is being prepared, as they add all insulin separately. Some organizations have worked to eliminate heparin as a PN additive, thus removing the potential for confusion with insulin.

**Dangerous Abbreviations and Dose Designations**

Errors have happened commonly with insulin and heparin when the word unit is abbreviated with a U. The U can easily be confused as a 0, a 7, or even cc when scripted. And U can look like a 0 even when typed. Similarly, when international unit is abbreviated IU, it has been seen as IV, resulting in some oral liquids being injected directly into the venous system. Neither of these abbreviations should ever be used under any circumstances as it has been responsible for fatalities and brain injuries due to insulin overdose or bleeding events due to heparin overdose.

Compounding errors due to leading zeros and trailing zeros are also frequently reported, and some have been associated with catastrophic results due to 10-fold overdoses when, for example, a decimal point is not seen when a number is less than 1 (eg, .2 mg may be seen as 2 mg) or when a trailing zero is used (1.0 seen as 10). For obvious reasons, all practitioners must take this issue very seriously. A complete list of dangerous abbreviations can be found at http://www.ismp.org/Tools/errorproneabbreviations.pdf. Also, ISMP guidelines for
Ineffective or Nonexistent Systems for Independent Checks

The ISMP is aware of fatal errors that reached patients because of IV admixture errors that were not detected during the checking process. In some of these cases, the operator’s work has gone unchecked. Whether PN is set up and prepared by a pharmacist or pharmacy technician is not what matters. What matters is that there is a method available to ensure sufficient quality control checks are made and documented 100% of the time.

Checks performed after manual IV admixture preparation often involve the “syringe pullback” method, particularly if the checking pharmacist is not consistently available in the IV clean room. To check each product added to a PN solution or chemotherapy bag, for example, the empty syringe used for each drug or electrolyte is left alongside the item with its plunger pulled back to the volume that was added.

Although the “syringe pullback” checking process is standard in many hospitals and even mentioned in USP Chapter <797>, it is less than ideal because the check is made after manual IV admixture preparation and is based on the preparer’s memory of how much product was added to the bag. Proper placement of the syringe next to the used product can also be problematic, particularly if the checking pharmacist is not consistently available in the IV clean room. To check each product added to a PN solution or chemotherapy bag, for example, the empty syringe used for each drug or electrolyte is left alongside the item with its plunger pulled back to the volume that was added.

In either situation, it is also important to include verification of the base solution and any premixed dilutions used to make the final preparation, as with neonatal/pediatric preparations, where a product is first diluted and then used as a stock bottle during daily preparations. It is also critical to require the checking pharmacist to verify the label and final preparation via comparison with the original order. The automated technologies mentioned above can make safer verification processes within reach of most hospitals.

Place each compounded preparation and associated supplies into a single bin/basket for checking, one at a time. Avoid bins/baskets with multiple compartments. Do not leave products on open counters for checking, even if they are well separated. Establish a system to communicate when compounded preparations are ready for checking, monitor the workflow, and provide assistance when necessary to avoid a backlog of preparations awaiting verification. Some hospitals use different-colored bins to signify steps in the process (eg, red bin for final preparations ready to be checked) or categories of solutions (ie, neonatal, pediatric, adult). Ensure the checking area is uncluttered, of sufficient size, and well lighted.

Dual-Chambered Bag Systems

On the market is a PN multichamber bag system with 1 chamber containing dextrose and the other chamber containing amino acids. A seal that separates the 2 chambers must be broken to mix the contents of both chambers together prior to dispensing. IV fat emulsion and electrolytes, vitamins, and trace elements are added as appropriate. There is also a similar product with electrolytes, and this can help to reduce medication preparation errors by lowering the risk of compounding calculations and minimizing the number of preparation steps. However, the ISMP has published previous reports where nurses or pharmacy staff have failed to activate or mix together the multichamber bags of PN solutions. The ISMP recommends that, wherever possible, these products not remain available in an automated dispensing cabinet or other
floor stock systems and other areas outside the pharmacy. Mixing should always be done prior to dispensing.

In hospitals without 24-hour service, PN should not be started after pharmacy hours, and dextrose alternatives should be available to provide replacement solution in emergencies until pharmacy service is available. Should an unusual circumstance exist, where product must be stored outside the pharmacy, they need to be accompanied by auxiliary labels (eg, “Mix Properly Prior to Administration”) and have instructions for mixing. The label could be applied to the overwrap near the port that will be spiked with tubing, to remind staff to mix the 2 chambers before administration. The manufacturer provides educational resources on its Web site (www.clinimix.com/pop-ups/video.jsp) that illustrate the multichamber bag technology and offer step-by-step bag activation training.

**Insulin and Tuberculin Syringe Measurement Errors**

The ISMP has received multiple error reports involving improper use of syringes to prepare insulin doses. These errors have been made by nurses, pharmacists, physicians, physician assistants, and so on. For example, when 7 units of insulin were needed, 0.7 mL (or 70 units with U-100 insulin) was drawn into a tuberculin syringe. In a recent article on insulin dosing mix, we described multiple cases where healthcare personnel were unfamiliar with proper use of the dose scale on insulin syringes, resulting in multiple overdoses and fatalities. Human error (eg, mental slips, lapses, forgetfulness) associated with insulin dose measurement is at issue.

With insulin, it must not be assumed that all healthcare practitioners are knowledgeable and skilled with measuring doses, preparing insulin infusions, and recognizing doses that exceed safe limits. Education regarding the concentration of insulin products, the differences between insulin syringes and other parenteral syringes, how to measure doses, recognition of safe dosage ranges, and how to administer the drug should be provided to all who might prepare PN solutions or administer insulin. Restrict insulin preparation and administration to those who have demonstrated competency. As always, require an independent double-check of all doses before dispensing and administering IV insulin.

**Special Handling of Electrolyte Additives**

Sending additives to the nursing unit or the patient’s home in syringes has posed some safety problems. In one incident, a poorly trained patient was sent syringes of potassium chloride to add to her son’s home PN upon detection of hypokalemia. Sadly, the mother injected the drug directly into the patient’s venous line, killing him almost instantly. Sending syringes for addition at home is a perilous practice for many reasons, not the least of which is the potential for misuse by caregivers who are not properly trained. Newly prepared solutions are a safer option.

Adding certain drugs to hanging IV containers can also present problems. With potassium chloride in particular, the additive may layer in the bottom of the IV bag close to the exit port. Thus, when infusion is resumed, a bolus of potassium chloride is inadvertently administered. Many nurses are not aware of this. Again, additives should not be added to PN solutions except under proper conditions in the pharmacy.

**Order Entry Errors**

Electrolytes in PN have been entered into the computer incorrectly. Often the basis for PN preparation in the IV compounding area is a label printed by the person inputting PN orders. However, no one else is actually making a second check of what was typed in by the order entry pharmacist. Thus, only one person actually has read the order, interpreted it, and entered it, and the other person is working off of that information. A second independent check is necessary, but a way to communicate the original scanned or electronic order must be available so that IV room staff do not need to leave their area. Standard label formats that list ingredients in the same order as PN order sets add efficiency and safety to the order entry process.

**Accidental Mix-ups Between Dosage Units**

Use of incorrect dosage units during ordering, order transcription, and/or labeling has been a routine cause for catastrophic errors. One example is an incident where an infant received a lethal dose of zinc stemming from an error that occurred during the order entry and compounding of a PN solution. The PN was prescribed for a preterm infant born at 26 weeks’ gestation. On the day of the event, the physician’s order included directions to add zinc in a concentration measured as mg/100 mL. Because the automated compounding used for PN required entry of zinc in a mcg/kg dose, the pharmacist converted the mg/100-mL dose to a mcg/kg dose. She performed this calculation correctly but accidentally entered the zinc dose in the pharmacy computer in mg, not mcg. This resulted in a final concentration in terms of mg/100 mL—a 1000-fold overdose.

Another pharmacist checked the work and preparation labels that were printed for compounding of the PN, but she did not notice the mcg to mg error. A pharmacy technician prepared the PN, replenishing the compounding syringe that contained zinc 11 times while preparing the solution, which required dozens of vials of zinc sulfate. The pharmacy computer order entry system and the automated compounder used to mix the PN did not alert the pharmacist that a 1000-fold overdose had been entered into the systems for the zinc additive. Upon discovery of the error, the infant received edetate calcium disodium (also referred to as calcium EDTA), which had been compounded by an external pharmacy, but the
chelation therapy was unsuccessful, and the infant died. The coroner listed cardiac failure caused by zinc intoxication as the cause of death.

To best prevent incidents like this, the method of ordering PN solutions for neonates, pediatric patients, and adults should be standardized so that each prescribed product and strength matches the dosing templates used for entering the orders into the computer system and automated compounder. Use pre-printed forms or standard order sets that list typical products and prompt the correct dosing method. On the rare occasions that calculations are necessary, require 2 clinicians to calculate the dose independently and compare their answers for verification.

This error happened at night when the PN was ordered. Policies that require prescribers to order PN daily during the day shift should be established and enforced to maximize safety with which these solutions are prepared and dispensed. Pharmacy staff should be aware of patients who are receiving PN and check if orders have not been received by the established time.

Continually emphasize to staff to complete a full review of the patient’s medications any time there is a need to use more than a few dosage containers (whether it be tablets, capsules, vials, ampuls, etc) to prepare or administer a single dose of any medication. In this case, use of 11 vials should have signaled that a catastrophic event may have been in process.

Safe Storage of Supplies
Separate the storage of concentrated bulk solutions, particularly concentrated electrolytes, amino acids, and dextrose, from all other products that are directly dispensed to a patient care unit. Among admixture supplies, also sequester sterile water for injection to reduce the risk of inadvertent use. When possible, employ small-volume vials of concentrated electrolytes for manual IV additives so that bulk bottles cannot be inadvertently used as base solutions or introduced back into the production line. In fact, it would be safest to use a vial size closest to the dose required to prepare the final preparation for any drug used in manual sterile compounding.

Error Reporting
Errors with PN or enteral nutrition (EN) should be reported to the ISMP MERP so that others may learn from near misses or actual PN-related errors. Although PN and EN are not traditionally thought of as medications, they are therapies that are prescribed, dispensed, and administered similar to medications. Administration also involves infusion devices that may be used in error. A.S.P.E.N. recommends that errors such as the ones described here be reported to the ISMP MERP. A special Web site location has been established for this purpose at www.nutritioncare.org/safety. The ISMP is a federally designated patient safety organization (PSO) that extends privilege and confidentiality protection for patient safety work product (information collected and created during the reporting and analysis of patient safety events).

Conclusion
Errors have occurred with PN ordering, transcribing, and compounding processes. Safe and standardized practices using organizational and regulatory guidelines must be used, and errors that do occur must be reported.

References
Safe Practices for Parenteral Nutrition

Task Force for the Revision of Safe Practices for Parenteral Nutrition:
Jay Mirtallo, MS, RPh, BCNSP, Chair,
Todd Canada, PharmD, BCNSP,
Deborah Johnson, MS, RN,
Vanessa Kumpf, PharmD, BCNSP,
Craig Petersen, RD, CNSD,
Gordon Sacks, PharmD, BCNSP,
David Seres, MD, CNSP, and
Peggi Guenter, PhD, RN, CNSN

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Special Report

Safe Practices for Parenteral Nutrition

Task Force for the Revision of Safe Practices for Parenteral Nutrition: Jay Mirtallo, MS, RPh, BCNSP, Chair, Todd Canada, PharmD, BCNSP, Deborah Johnson, MS, RN, Vanessa Kumpf, PharmD, BCNSP, Craig Petersen, RD, CNSD, Gordon Sacks, PharmD, BCNSP, David Seres, MD, CNSP, and Peggi Guenter, PhD, RN, CNSN

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NOTICE: These A.S.P.E.N. Practice Guidelines for Safe Practices for Parenteral Nutrition are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of providing parenteral nutrition feeding formulations. The underlying judgment regarding the propriety for any specific practice guideline or procedure shall be made by the attending health professional in light of all the circumstances presented by the individual patient and the needs and resources particular to the locality. These guidelines are not a substitute for the exercise of such judgment by the health professional, but rather are a tool to be used by the health professional in the exercise of such judgment. These guidelines are voluntary and should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed toward obtaining the same result.

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GLOSSARY OF TERMS

Automated Compounding Device: A device used in the preparation of parenteral nutrition. It automates the transfer of dextrose, amino acids, fat emulsion, and sterile water, as well as small volume injectables, such as electrolytes and minerals to the final PN container. The device is driven by computer software.

Beyond-use Date: The date established by healthcare professionals from the published literature or manufacturer-specific recommendations beyond which the pharmacy-prepared product should not be used.

Compatibility: The ability to combine 2 or more chemical products such that the physical integrity of the products is not altered. Incompatibility refers to concentration-dependent precipitation or acid-base reactions that result in physical alteration of the products when combined together.

Computerized Prescriber Order Entry (CPOE): A prescription ordering system where the prescriber enters orders directly into a computer.

DEHP: Di (2-ethylhexyl) phthalate, a plasticizer used in various intravenous administration sets or plastic infusion bags.

Dosing Weight: The weight used by the clinician in determining nutrient doses. Dependent on institutional or professional preference, the dosing weight may be the actual, ideal or adjusted body weight of the individual.

Drug-nutrient Interaction: An event that occurs when nutrient availability is altered by a medication, or when a drug effect is altered or an adverse reaction caused by the intake of nutrients.

Dual-chamber Bags: A bag designed to promote extended stability of a PN formulation by separating the IVFE from the rest of the formulation. It consists of 2 chambers separated by a seal or tubing that is clamped. At the time of administration, the seal or clamp is opened to allow the contents of both chambers to mix and create a TNA.

Expiration Date: The date established from scientific studies to meet FDA regulatory requirements for commercially manufactured products beyond which the product should not be used.

Hang Time: The period of time beginning with the flow of a fluid through an administration set and catheter or feeding tube and ending with the completion of the infusion.

Institute of Safe Medication Practices (ISMP): A nonprofit organization that works closely with healthcare practitioners and institutions, regulatory agencies, professional organizations and the pharmaceutical industry to provide education about adverse drug events and their prevention. The Institute provides an independent review of medication errors that have been voluntarily submitted by practitioners to a national Medication Errors Reporting Program (MERP) operated by the United States Pharmacopeia (USP).

Intravenous Fat Emulsion (IVFE): An intravenous oil-in-water emulsion of oil(s), egg phosphatides and glycerin. The term should be used in preference to lipids.

MEDMARX: The internet-based medication error reporting program operated by the U.S. Pharmacopeia that complements quality improvement activities at the local and national level. MEDMARX is available through subscription service only.

Osmolarity: The number of osmotically active particles in a solution, expressed as milliosmoles per liter of solution. The osmolarity of a PN formulation needs to be considered, when determining whether that solution can be administered through a peripheral vein.

Parenteral Nutrition: Nutrients provided intravenously.

Central: Parenteral nutrition delivered into a high flow vein, usually the superior vena cava adjacent to the right atrium.

Peripheral: Parenteral nutrition delivered into a peripheral vein, usually of the hand or forearm.

Percent Concentration (weight/volume): A standardized unit of concentration determined by the amount of drug or nutrient within a given volume, whereby 1% (w/v) is equivalent to 1 g of drug or nutrient per 100 mL of volume.

Stability: The extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture.

Total Nutrient Admixture (TNA): A parenteral nutrition formulation containing IVFE as well as the other components of PN (carbohydrate, amino acids, vitamins, minerals, trace elements, water and other additives) in a single container.

Medication Error Reporting Program (MERP): U.S. Pharmacopeia’s spontaneous reporting program for medication errors that is operated in cooperation with the Institute for Safe Medication Practices for use by any healthcare professional or interested party.

Venous Access Devices (VAD): Catheters placed directly into the venous system for infusion therapy and/or phlebotomy.

PREFACE

The members of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) are health care professionals representing the fields of medicine, nursing, pharmacy, and dietetics. A.S.P.E.N.’s mission is to serve as the preeminent, interdisciplinary nutrition society dedicated to patient-centered, clinical practice worldwide through advocacy, education, and research in specialized nutrition support.

Patients may be treated with parenteral nutrition (PN) in any of several care settings including hospitals, long-term care or rehabilitation facilities, or at home. Because patients transfer from one health care environment to another, it is the opinion of the A.S.P.E.N. Board of Directors that the practice guidelines in the
“Safe Practices for Parenteral Nutrition” are the standard of practice for the provision of PN in all healthcare settings.

The original ‘Safe Practice’ document was specific to PN and the practice of pharmacy. The objective of this revision is to deal with PN in a comprehensive manner realizing the interdisciplinary nature of this therapy. A new section is added that addresses the ‘ordering of parenteral nutrition’. The nutrient range section is expanded to provide dosage recommendations that go beyond normal requirements and include components not addressed in the initial guidelines (e.g., iron and the potential for developing an essential fatty acid deficiency). Further, the PN filtration section is renamed and expanded into: “Administration of parenteral nutrition”. This section includes hang time for intravenous fat emulsion (IVFE) and PN, formula review prior to administration as well as institutional use of PN brought from home or sent with the patient on transfer from another facility.

Unfortunately, practice for some of these latter areas have little, if any, published evidence to support good practice. As such, the Task Force conducted the 2003 Survey of PN Practices. This provided an overview of the variance and consistency of current practices. The survey was organized in the following sections: demographics, writing PN orders, computer order entry of PN orders and problems with PN orders. There were 667 responses, mostly from hospitals (85%), with dietitians (55%) and pharmacists (32%) being the predominant professionals responding to the questionnaire. In the home health care environment, responses were from pharmacists (76%) and dietitians (17%). The average daily census for organizations responding was 100 patients. Most organizations used a once daily nutrient infusion system (76%). The number of adult PN patients per day was from 0–20 for 85% of responders. However, 4.9% of responders reported more than 40 adult PN patients per day. For organizations that had neonate and pediatric patients, the number of PN patients per day was 0–5 for both.

Over half (54%) of responders had a performance improvement program that monitored the appropriate use of PN, accuracy of PN orders, metabolic complications and catheter and infectious complications. Physicians and nurses selected these categories more frequently than pharmacists and dietitians. Quality control of PN compounding and PN costs were not monitored as frequently (<50%).

It was noted that physicians were the professional group responsible for writing PN orders. However, there was also significant involvement by dietitians as well as pharmacists. It is noteworthy that nurse practitioners and physician assistants were also involved with writing PN orders. Oversight of writing the PN order was performed predominantly by the pharmacist with significant involvement by the pharmacist. For PN components, the base formula was ordered in terms of percent final concentration (47%) or as the percent of stock solution (31%). There is no consistent method of ordering PN electrolytes. Phosphorus is usually ordered as millimoles (mmol) of phosphorus or as both mmol of phosphorus and milliequivalents (mEq) of associated cation. Electrolytes as components of the amino acid formulation were not usually considered when writing PN orders (71%). Multiple electrolyte formulations were used in 62% of organizations, according to the summary of responses, but only 46% of the time according to the pharmacist response (in this case, the pharmacist response should be more accurate). In 62% of responders, the pharmacist adjusts the chloride and acetate content of the PN formulation. Trace elements are ordered as a standard volume (87%) with only some organizations adjusting the content based on the patient’s clinical condition (22%). Standard order forms are used by 87% of responders of which 96% are for adults and 40–42% are for pediatric and neonatal patients. Home infusion services are the outlier in this group where standard order forms are used in only 32% of organizations. Standard orders for laboratory tests and patient care orders are used in only 54% of cases. Data for the hang time or maximal infusion rate of IVFE were more difficult to interpret since a write-in answer was required. The maximum hang time for a total nutrient admixture (TNA) was 24 hours and intermittent, separate IVFE infusion of 12 hours. Responses to minimum hang time (related to maximal infusion rates) were not consistent.

Only 29% of organizations used a computerized prescriber order entry (CPOE) system for PN orders. Of these, 88% used it for adults and 54% and 58% used it for pediatric and neonatal patients. The majority of pharmacies (88%) used an automated compounding device. Order input to the automated compounding device was done by the pharmacist 84% of the time due to a lack of an interface with the CPOE system. Only 15% of organizations outsourced PN formulations. Of those that did, a pharmacist at the organization reviewed the order where the order originated (95%) prior to it being sent to the compounding pharmacy.

Problems with PN orders were queried in the following manner; number of PN orders written per day, percent of orders requiring clarification, reasons orders needed to be clarified, frequency of errors in PN therapy, categories of PN adverse events and severity of adverse events. Most (55%) organizations deal with 0–10 PN orders per day while 15% had more than 30 orders per day. These orders need to be clarified <25% of the time for 88% of responders and <10% of the time for 61% of responders. The most frequent reasons orders need to be clarified are macronutrient content, illegible orders, incompatibility, nutrient dose outside the normal range, infusion rate not prescribed and incorrect PN volume. Seldom, if ever, were orders clarified for a pharmacy compounding error. The highest ranked reason, very often (5% of responders) was illegible orders. The frequency of reported errors per month for PN was low (none in 26%, 1–5 in 60% and 6–10 in 10% of responders). These errors were related to electrolytes (69%), dextrose (31%), insulin (31%), amino acids, vitamins and IVFE (15% and 26%). Of these errors, 55% of responders related them to errors in ordering PN in the category of 1–25%, 12% in the 26–50% category, 8% in the 51–75% category and 17%
in the 76–100% category. For adverse events that had occurred in the last 2 years, 44% of responders were not aware of any events, 64% of the events required no treatment or just an increase in monitoring. Only 10% responded that none of these events occurred. Of interest are the reports by a few responders of harm, temporary (13%, N = 61 responders) or permanent (2%, N = 7 responders), near-death (3%, N=16 responders) or death (2%, N = 7 responders). Whether hospitals allowed PN formulations compounded by organizations other than their own was queried and results were mixed (43% - Yes, 58% - No).

Realizing that the original Safe Practice guidelines are not consistently implemented,2 the Task Force used this information to identify practices pertinent to the revision of the Safe Practice guidelines. The survey results presented in this document are those findings pertinent to the development of the guideline. A more in-depth and complete analysis of the 2003 Survey of PN Practices will be conducted and reported by the Task Force within the next year. This snapshot of current practices and expert opinion or consensus provided by both external and internal reviews was compiled into the current Safe Practices.

Guidelines will be presented in a format similar to the A.S.P.E.N. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patient.3 “Safe Practices for Parenteral Nutrition” is organized into seven sections.

- Introduction
- Ordering parenteral nutrition
- Labeling parenteral nutrition formulations
- Nutrient requirements
- Sterile compounding of parenteral nutrition formulations
- Stability and compatibility of parenteral nutrition formulations
- Parenteral nutrition administration

Each section includes an introduction to the practice area addressed, with examples where clinical data (including patient harm) support the need for practice guidelines to ensure patient safety; specific practice guidelines based on consensus of the Task Force members; summary of areas requiring special consideration; and a list of supporting references.

The members of the Task Force for the Revision of Safe Practices for Parenteral Nutrition are as follows:

Chairman:
Jay Mirtallo, MS, RPh, BCNSP
The Ohio State University Medical Center
Columbus, Ohio

Todd Canada, PharmD, BCNSP
The University of Texas, MD Anderson Cancer Center
Houston, Texas

Deborah Johnson, MS, RN
Meriter Hospital
Madison, WI

Vanessa Kumpf, PharmD, BCNSP
Nutrishare, Inc
Elk Grove, CA

Craig Petersen, RD, CNSD
University of California Davis Medical Center
Sacramento, CA

Gordon Sacks, PharmD, BCNSP
University of Wisconsin
Madison, WI

David Seres, MD, CNSP
Albert Einstein College of Medicine
New York, NY

Peggi Guenter PhD, RN, CNSN
A.S.P.E.N.
Silver Spring, MD

This document was internally reviewed by the A.S.P.E.N. Standards Committee as well as the Dietetic, Nursing, Medical, and Pharmacy Practice Sections and approved by the A.S.P.E.N. Board of Directors after external review by individuals and other associations of health care professionals. A.S.P.E.N. recognizes that the practice guidelines will have broad ramifications in changing clinical practice in many health care settings for pharmacists, physicians, nurses, dietitians, and technical support personnel. It is hoped that these guidelines will be accepted and used to prevent future patient harm, and will serve as a catalyst for future research.

REFERENCES

SECTION I: INTRODUCTION

Over the past four decades, parenteral nutrition (PN) has become an important primary (e.g., intestinal failure) and adjunctive therapy in a variety of disease states. Parenteral nutrition refers to all PN formulations; total nutrient admixtures (TNA) are PN formulations that include intravenous fat emulsions (IVFE); and 2 in 1 formulations are PN formulations that do not include IVFE. PN benefits patients having significant disruption in gastrointestinal (GI) function becoming a lifeline for those who have a permanent loss of the GI tract such as patients with GI fistulas or short bowel syndrome. New knowledge and technology have improved patient selection for PN therapy. Refinement of PN will continue to make it a useful therapy in the management of patients with dysfunctional GI tracts. However, PN formulations are
extremely complex admixtures containing 40 or more components including amino acids, dextrose, fat emulsions, water, electrolytes, trace elements, and vitamins. Each of these components is a regulated prescription drug product. Serious harm and death have occurred from improperly prepared and administered PN formulations. With a potential for significant benefit to many patients, its complexity warrants an effective process of ordering, preparation, administration and monitoring to assure a quality outcome from therapy. Early PN programs focused on minimizing the frequency, severity, and type of complications that could result from this therapy. The interdisciplinary approach was found to improve efficacy, reduce complications, and facilitate efficient, cost-effective PN therapy. Despite the highly successful use of PN for many years, the following adverse events demonstrate the types of PN errors that can result in serious harm and even death:

- Two deaths related to errors in PN compounding led to a Safety Alert being issued by the U.S. Food and Drug Administration (FDA). Autopsy of the patients involved found diffuse microvascular pulmonary emboli. There were also at least two other cases of respiratory distress occurring in patients at the same institution. These patients had received total nutrient admixtures (TNA) thought to contain a precipitate of calcium phosphate that resulted from improper admixture practices in the pharmacy.
- Hospital personnel misinterpreted the dextrose content on the label of a PN formulation used in home care, which resulted in a pediatric patient’s death. The home care label read: “300 mL of 50% dextrose.” The hospital pharmacy interpreted this as a final concentration of dextrose 50% (up to twice the concentration typically used in PN therapy). The patient died after 2 days of receiving infusion of the incorrect formula.
- Two other fatal incidents have been reported involving pharmacy-compounding operations for pediatric dextrose solutions. One infant was overdosed with dextrose when the PN was prepared with amino acids and two bags of 50% dextrose in place of one bag of 50% dextrose and one bag of sterile water. The other infant was underdosed with dextrose while receiving a 1.75% final concentration of dextrose solution rather than a 17.5% concentration.
- Another PN formulation was compounded with no dextrose, resulting in irreversible brain damage when administered to a neonate.
- An incident involving the misinterpretation of a label resulted in iron overload and liver toxicity in a child receiving PN with iron dextran. In this case, the PN label read, “iron dextran 1 mL,” the intention being to use a 1-mg/mL concentration prediluted by the pharmacy. However, the solution containing the undiluted, 50-mg/mL concentration was used in compounding and resulted in a 50-fold error in the dose administered.
- Four children were infected, two of whom died as a result of receiving contaminated PN admixtures. Enterobacter cloacae was cultured from disposable tubing that was used in the automated compounding of these PN admixtures.
- A 2-year old child receiving home PN died after an excessively high level of potassium was identified in the PN formulation. The most likely explanation provided for the death was human error in the manual preparation of the PN formulation.
- Two premature infants developed extreme magnesium toxicity while receiving PN that was the result of an automated PN compounder malfunction.
- PN has the potential for serious adverse events involving many PN components as well as system breakdowns. Analysis of data reported to the United States Pharmacopoeia Medication Error Reporting Program (MERP), presented in cooperation with the ISMP, and the MEDMARX medication error database suggests that PN events are low in frequency but have the capacity to cause patient harm. Errors were related to wrong drug preparation, improper dose, labeling and problems with automated compounding devices. The PN components most commonly associated with errors were electrolytes, concurrent drug therapy, insulin and dextrose. It is unclear what proportion of actual PN-associated errors are actually reported to the USP.

The information provided in the ‘Safe Practices for Parenteral Nutrition’ document provides guidelines along with supporting evidence to foster quality PN therapy. The intent is for the principles provided in the document to become incorporated into healthcare organization practice for the purpose of minimizing the risk of PN. The complexity of this therapy cannot be understated. There is good evidence in support of practices that favor positive patient outcomes.

REFERENCES
9. The U.S. Pharmacopeia Center for the Advancement of Patient Safety medication error reporting programs—MEDMARX and the Medication Errors Reporting Program.

SECTION II: ORDERING PARENTERAL NUTRITION

BACKGROUND

As reported in the introduction to this document, life-threatening errors continue to occur in the preparation and delivery of PN admixtures to patients. Many of the errors that occur are related to the order-
ing process. Responses to the 2003 Survey of PN Prac-
tices confirm a lack of uniformity in the ordering pro-
cess from institution to institution, and clinical errors
were frequently related to the manner that orders were
created and communicated, as well as incorrect units of
measure, and errors of omission.

Research has demonstrated the benefit of standard-
ized order writing processes in reducing prescription
errors.1–3 Standardized PN order forms:

- Incorporate more precise guidelines for PN prescrib-
ing, including standing orders for PN initiation and
discontinuation2–4,6–7.
- Provide physician education,2–4,6–7 especially impor-
tant for clinicians unfamiliar with PN therapy.
  - Reduce prescribing errors by a range of 9% to
22%,1,2,4,6,7 primarily by reducing the incidence of
incompatible concentrations of electrolytes, inap-
propriate concentrations of dextrose, amino acids
and IVFE, and omissions of nutrients.
- Improve efficiency and productivity of nutrition
support, primarily in hospitalized patients.1,3,6 The
rate of total calorie and protein overfeeding was
decreased by 18%, imparting a 55% reduction in
the cost of processing and preparation of an initial
PN order for a standardized solution.
- Allow comprehensive nursing and dietary care of the
patient2,6,8 by reducing nursing order interpretation
problems and improving documentation of each bag
administered.
  - Reduce pharmacy inventory and costs1,3,6,7,9–11 by
reducing PN wastage, standardizing PN solutions,
and implementing pharmacy formulary control of
various amino acids and IVFE products, resulting
in annual savings from $10,000 to $76,803.

It should be noted that one study reported an
increase in prescriber errors after a standardized PN
form was introduced. Problems occurred with PN infu-
sion rates, electrolyte composition, and amino acids
centration, when using a standardized PN order
form.2 Therefore, creating and maintaining a stan-
dardized PN order form that meets the needs of
patients and minimizes errors still requires a continual
quality assurance effort and patient safety commit-
ment by each institution.

Common factors associated with the majority of PN
prescribing errors include:12

- Inadequate knowledge regarding PN therapy
- Certain patient characteristics related to PN therapy
  (e.g., age, impaired renal function)
- Calculation of PN dosages
- Specialized PN dosage formulation characteristics
  and prescribing nomenclature

Parenteral nutrition has been reported to be second
only to anti-infective agents as a class of medications
associated with errors (22% of reports).12 Education
was cited as necessary for successful implementation
in most published reports. Therefore, the PN order
form shall be designed to serve as an educational tool
for prescribers.2–4,6,7

Finally, to minimize errors in all prescription prac-
tices, accrediting bodies,13 USP,14 the National Coor-
dinating Council for Medication Error Reporting and
Prevention15 and the Institute for Safe Medication
Practices (ISMP)16 have made recommendations for
medical documentation. These recommendations spec-
ify avoiding potentially dangerous abbreviations, acro-
nyms and symbols.

A set of minimum standards for creating a PN order
are herein recommended, based on these principles
and published clinical experiences and best practices,
in order to reduce errors and improve patient safety.
These standards are a result of a review of the litera-
ture. A review of PN order forms submitted by survey
responders aided in identifying components of PN
order forms that were universally acceptable to most
institutions. The standards are divided into three sec-
tions, Mandatory for Inclusion, Strongly Recom-
pended for Inclusion, and Worthy of Consideration for
Inclusion (Table I).

MANDATORY FOR INCLUSION

Overall Design: Clarity of the Ordering Form

Order forms shall be created in such a way as to be
understandable to all healthcare professionals who
interact with the form, including the ordering cli-
nicians and staff interpreting the PN order (dietitian,
nurse and pharmacist). The following are specific prin-
ciples recommended to promote order form clarity:

**Organization.** The form shall be organized in a simple manner. All nutrients in PN, as well as final volume, and infusion duration, shall be clearly identified on the form. Final volume shall be the sum of all components of the PN solution, including IVFE in a TNA. The process of entering specific components on the order shall follow an obvious visual pathway, making it easy to scan for completeness.

**Institutional policies.** The form shall contain enough information to address anticipated institutional policies and procedures. Institution-specific concerns shall be incorporated into the order form as written instructions. For example, institutional policies may specify that certain clinical requirements be met, such as specific diagnoses or the completion of baseline laboratory tests, before PN is prepared by the pharmacy.

**Continuity.** The PN order form shall list all components in the same format (e.g. amount per day and in the neonatal or pediatric patient, both amount/day and amount/kg/day) and sequence as the PN label (described in Section III). In keeping with labeling guidelines, electrolytes shall be ordered as the quantity of associated salt to be added to the PN formulation. This will facilitate the verification of the PN contents against the PN order.

**Writing the order.** The use of a standardized PN order form will reduce the need for prescriber handwritten items, thus, potentially reducing misinterpretation. However, adequate space for clear handwriting shall be provided where needed. The use of decimals and trailing zeroes shall be avoided whenever possible. Orders containing unclear handwriting, or other incorrect or confusing marks, shall not be compounded until the pharmacy has clarified these with the clinician generating the order.

**Units of measure.** The form shall be designed using standard units of measure (e.g. protein in grams, potassium in mEq, and phosphate in mmol) for dosing PN components. Review of sample PN order forms submitted to the Task Force found doses of macronutrients expressed in different units on the same order form (e.g. dextrose in calories, protein in grams and fat as volume of a specific concentration). The use of percent concentration in PN orders is not recommended, to avoid confusion. Misinterpretation of orders using percent concentration has led to patient harm and death.

**Specific Components**

The following are items considered to be mandatory for inclusion on the PN form. They include both data to be collected on the form, as well as information that must be communicated to the clinician ordering the PN. It is assumed that areas for ordering the necessary components of the PN (dextrose, protein, IVFE, electrolytes, vitamins, minerals, etc) will be incorporated into the form.

- For the purpose of clarifying unclear or inappropriate orders, the PN order form shall provide contact information for the person writing the PN order. There shall also be a space on the form for the contact information of institutional resources, such as individual consultants or a nutrition support service.
- The order form shall specify the time by which PN orders need to be submitted for pharmacy processing. The specified deadline should be chosen by the institution to assure adequate time for a comprehensive order review, safe compounding, and scheduled delivery of the PN formulation. There shall also be a standardized hang time specific to each institution. The preparation and hang time of each PN solution that is not refrigerated should not exceed 30 hours due to stability concerns. Additionally, all components of the PN order form shall be completed in their entirety when reordering for an existing patient. Each institution shall dictate the frequency of PN reordering (e.g., daily).
- The PN order form shall contain the location of the venous access device, in order to assure that venous access is appropriate for the osmolarity (Table II) of the ordered PN formulation. A checkbox on the order form may be used to denote whether the catheter tip lies in a peripheral or central venous position, and whether position has been confirmed by x-ray for central venous catheters.
- The order form shall contain fields for patient height, dosing weight, and PN indication. Knowledge of patient dosing weight is vital in assessing nutrient needs and identifying nutrient dosing errors, especially in the pediatric population, where total nutrient dosing varies dramatically based upon weight.
- Institutional policy for maximum or minimum nutrient hang times (and corresponding infusion rates), maximum dextrose infusion rate or IVFE infusion rate, or maximum allowable hang time for separately infused IVFE, if 2-in-1 solutions are utilized, shall be indicated on the order form. Written infusion instructions for either 24-hour or cycled PN must comply with institutional policies.
- The PN order form shall contain a general statement warning of the potential for PN formulation incompatibilities. Calcium and phosphorus compatibility shall be specifically addressed, as it is common for prescribed concentrations of these nutrients to exceed PN solubility limits, which may result in patient harm or death from calcium phosphate precipitates instigating diffuse microvascular pulmonary emboli.
STRONGLY RECOMMENDED FOR INCLUSION

These items, although not mandatory, are strongly recommended for inclusion on the PN order form (or back of the form):

- Basic PN education tools to guide prescribers in creating an appropriate initial order with maximum dosage recommendations for peripheral or central infusion and for various ages or weights for pediatrics.
- Example calculations to guide prescribers in determining patient-specific total calories, protein, fluid, and electrolyte requirements. This should also include the recommended ranges for these nutrients (e.g., dextrose and IVFE infusion rates).
- Guidelines for ordering appropriate baseline laboratory tests, including levels requiring daily (e.g., potassium, glucose) or less frequent monitoring (e.g., liver enzyme tests).
- Guidelines for stopping or tapering of PN, to avoid rebound hypoglycemia and to provide patient safety in the event of this complication.
- Specific contents of commercial multivitamin and trace element preparations available within the prescribing institution, with daily age-specific recommendations.
- Brand names of products, such as amino acids or IVFE, available at the prescribing institution, with specific characteristics of these products (e.g., pH, phosphate content).
- Specific guidelines for the use of insulin, including the type appropriate for inclusion in the PN solution (e.g., regular insulin). Insulin guidelines should be institution-specific to age and patient populations served.
- Guidelines for recognizing additional sources of calories (e.g., fat emulsion vehicle for propofol [Diprivan®] infusions, dextrose in IV solutions).

WORTHY OF CONSIDERATION FOR INCLUSION

Several additional items are felt to be helpful, but of less importance in the order writing process. Due to the number of items felt to be mandatory or strongly recommended, these items are presented as suggestions for inclusion where room and organization of the order form will allow.

- Persons involved in reviewing the order, other than the prescriber and the pharmacist, may be identified for ease of contact and continuity. This may be helpful when an institution utilizes a clinician or committee to oversee the quality or appropriateness of PN orders.
- Guidelines for nutrient restriction or supplementation in various disease states, such as restriction of copper in hepatic failure, may be included. These recommendations should follow published clinical guidelines.
- PN therapy in acute care institutions is on average 10–14 days in duration.21 Guidelines for long-term PN administration may be beneficial when therapy is for extended periods of time in the acute care or alternative care setting. These may include, for example, recommendations for monitoring or supplementation that is specific to long-term PN patients. These guidelines should also address the use of cyclic versus continuous PN infusion. Persons without advanced knowledge in nutrition support may not be familiar with the utility, or more accurately the general lack of utility, of specialty amino acids. Therefore, guidelines for the use of these formulations may be helpful.

ADULT PN ORDER FORM TEMPLATE (FIG. 1)

A sample PN order form template has been created to facilitate a standardized ordering process among institutions and facilities preparing PN formulations. The Task Force does not endorse a specific PN dosage regimen or formulation. A few points about the sample PN order form template should be clarified:

- A field for allergies is included on the form so that potential adverse reactions to heparin, IVFE products, latex components of parenteral products, or bisulfites can be averted.
- The units of measure for the peripheral IV administration route are designated in mOsm/L, since the decision for central or peripheral PN administration should be dictated by the total osmolarity of the PN formulation, rather than solely on final dextrose or amino acids concentration.
- A field for laboratory tests and monitoring information is provided, so that fluid and electrolyte imbalances and signs/symptoms of CVC infections can be assessed. Specific monitoring parameters used to determine the efficacy or detect complications of PN therapy are not listed on the form. Laboratory values such as visceral proteins, CBC with differential, or PT/PTT, are not included on the form, since the necessity or frequency for obtaining these tests varies between institutions and facilities.
- The amount per day of macronutrients (i.e., dextrose, protein, fat) is not specified on the form. Many facilities have developed “standardized” formulations for use within their healthcare organizations to improve the efficiency and productivity during the preparation process. Standardized PN dosage formulations may be included on institution-specific order forms. Inclusion of a blank field is recommended so that a formulation can be customized for nutrient restriction or supplementation in various disease states.
- For illustration purposes only, both a 2-in-1 and a TNA formulation are listed on the form. Realizing most institutions utilize only one type of delivery system (e.g., 2-in-1 vs. TNA), it is not necessary to list both of these PN formulations on the order form.
- If a facility only uses TNA formulations, it is not necessary to include maximum hang times or infusion rates for separately infused IVFE.
- The “Additives Section” is specifically designed to separate the field for regular insulin from the other additives. Responses to the 2003 Survey of PN Practices indicated that doses for other additives (especially H2 antagonists) were misinterpreted for insulin dosages when the field for regular insulin was placed in close proximity to other additive fields on
FIG. 1

**Physician Orders**

**PARENTERAL NUTRITION (PN) - ADULT**

<table>
<thead>
<tr>
<th>Primary Diagnosis:</th>
<th>Ht: ______ cm Dosing Wt: ______ kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN Indication:</td>
<td>Allergies: ______________________</td>
</tr>
</tbody>
</table>

**Instructions:** This form must be completed for a new order or continuation of PN and faxed to the Pharmacy by [Insert Time] to receive same-day preparation. PN administration begins at [Insert Time]. Contact the Nutrition Support Service at (XXX) XXX-XXXX for additional information.

**Administration Route:**
- [ ] CVC or PICC Note: Proper tip placement of the CVC or PICC must be confirmed prior to PN infusion
- [ ] Peripheral IV (PIV) (Final PN Osmolarity ≤ ______ mOsm/L)

**Monitoring:** Daily weights, Strict input & output, Bedside glucose monitoring every _____ hours
- [ ] Na, K, Cl, CO₂, Glucose, BUN, Scr, Mg, PO₄ every ________________
- [ ] T. Bili, Alk Phos, AST, ALT, Albumin, Triglycerides, Calcium every ________________

**Base Solution:** Parenteral nutrition MUST be administered through a dedicated infusion port and filtered with a 1.2-micron in-line filter at all times. Discard any unused volume after 24 hours.

<table>
<thead>
<tr>
<th>Select one</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Dextrose 2-in-1</td>
<td>☐ CENTRAL 2-in-1</td>
</tr>
<tr>
<td>Dextrose _____ g</td>
<td>Dextrose _____ g</td>
</tr>
<tr>
<td>Amino Acids (Brand ______) _____ g</td>
<td>Amino Acids (Brand ______) _____ g</td>
</tr>
<tr>
<td>For patients with PIV and established glucose tolerance: Provides ______ kcal; Maximum Rate not to exceed ______ mL/hour</td>
<td>For patients with CVC or PICC and established glucose tolerance: Provides ______ kcal; Maximum Rate not to exceed ______ mL/hour</td>
</tr>
</tbody>
</table>

**RATE & VOLUME:** _____ mL/hour for _____ hours = _____ mL/day

Must specify

or CYCLIC INFUSION: _____ mL/hour for _____ hours, then _____ mL/hour for _____ hours = _____ mL/day

**Fat Emulsion (Brand ______) – via PIV or CVC with 2-in-1 base solutions** (Select caloric density & volume)

<table>
<thead>
<tr>
<th>10%</th>
<th>250 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

(Note: Infusions < 4 or > 12 hours not recommended)

**Additives:** (per day)

<table>
<thead>
<tr>
<th>Sodium Chloride</th>
<th>as Acetate</th>
<th>as Phosphate</th>
<th>Potassium Chloride</th>
<th>as Acetate</th>
<th>as Phosphate</th>
<th>Calcium Gluconate</th>
<th>Magnesium Sulfate</th>
<th>Adult Multivitamins</th>
<th>Adult Trace Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq</td>
<td>mEq</td>
<td>mmol of PO₄</td>
<td>mEq</td>
<td>mEq</td>
<td>mmol of PO₄</td>
<td>mEq</td>
<td>mEq</td>
<td>mL/day</td>
<td>mL/day</td>
</tr>
</tbody>
</table>

**Normal Dosages**

**Additives:** (per day)

<table>
<thead>
<tr>
<th>Regular Insulin</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend if hyperglycemic, start with 1 unit for every 10 g of dextrose</td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacy Use Only:** Ca/PO₄ Limit Checked __________

**Note:** Some brands of amino acids contain phosphates

**Physician’s Signature:** ___________ **Paging Number:** ___________ **Date/time:** ___________

**Orders transcribed by:** ___________ **Date/time:** ___________ **Orders verified by:** ___________ **Date/time:** ___________
the form. To prevent errors and promote clarity in ordering regular insulin, an attempt should be made to separate this field from other additives.

- Although not depicted in the sample PN order form template, basic PN education tools should be included on the back of the form to assist prescribers in correctly filling out the form. Information such as nutrient dosage recommendations, example calculations, specific contents of multivitamin and trace element preparations, and dosing recommendations for insulin can be helpful to the prescriber during the order writing process.

The format for a Pediatric PN order form would be very similar to the Adult PN order form template except the fields for macro- and micronutrients are specific for age or weights of the pediatric patients.

PRACTICE GUIDELINES

1. Standardized order forms (or order entry screens) shall be developed and designed for adult and pediatric PN formulations to aid prescribers in meeting the estimated daily patient nutritional requirements and improve order clarity.

2. The clinician and compounding pharmacist shall assess the PN formulation to determine whether its contents are within an acceptable standard range based on the specific patient population (e.g., adult or pediatric). They shall also assess whether a clinical disease state or condition warrants a dose outside the standard range.

3. The use of percent concentration in PN orders should not be used. The use of total daily dose is encouraged.

4. Potentially dangerous abbreviations and dose expressions should be avoided. Specifically:
   - Do not use trailing zeros (e.g. 5 mg, and not 5.0 mg)
   - Use leading zeros for doses less than one measurement unit (e.g. 0.3 mg and not .3 mg)
   - Spell out the word UNITS (e.g. never U which could be easily mistaken as a zero)
   - Spell out routes of administration and all intended instructions.

5. All components of the PN order must be re-written when PN is reordered.

Special Considerations

According to the 2003 Survey of PN Practices, the computerized prescriber order entry (CPOE) system for PN orders is used in only 29% of organizations surveyed. The best CPOE method or process for PN orders is not yet described in the literature. Converting standard paper orders to the computer creates unique problems when an adjusted or dosing weight that is different from the patient’s actual or admission weight is used when calculating caloric and protein requirements.

REFERENCES


SECTION III: LABELING PARENTERAL NUTRITION FORMULATIONS

BACKGROUND

The manner in which PN ingredients are labeled varies considerably1. PN base components (dextrose, amino acids, and IVFE) are labeled as mmol or mEq per liter or per volume. For example,
sodium chloride (NaCl) in a dose of 80 mEq/L admixed in a PN with a volume of 2 liters may be labeled as follows:
- NaCl 80 mEq/L
- NaCl 160 mEq per total volume
- Na 80 mEq/L, Cl 80 mEq/L
- Na 160 mEq and Cl 160 mEq per total volume.

This lack of standardization causes a great deal of confusion when patients are transferred between healthcare environments. As such, an essential component of a patient transfer between healthcare environments is a pharmacist-to-pharmacist interaction to resolve potential problems with transfer of the prescription. Misinterpretation of a PN label that led to a patient death^2 exemplifies what may occur if this interaction does not occur. To avoid misinterpretation, the labels for PN formulations should be standardized. All PN labels in any health care environment shall express clearly and accurately what the patient is receiving at any time.

Each method of labeling has distinct advantages and disadvantages. The use of the percent of original dextrose or amino acid concentration is specific for the product used by the pharmacy in compounding the PN formulation. However, interpretation of this label requires knowledge of pharmaceutical calculations in order to determine the nutrient value of the PN formulation. This involves training professionals in several health care disciplines to determine the nutrient value of the PN admixture being administered. Using the percent of final concentration of dextrose, amino acids, or IVFE still requires calculations to determine the caloric value or dose being administered, but it is traditionally the most accepted type of label because it is consistent with the label of the original commercial product as shipped from the manufacturer. To minimize calculation errors and provide a label more consistent with dispensing a PN formulation as a nutrient, some programs have used grams of base components per liter. This simplifies the conversion of the nutrients to calorie and gram doses being provided, but still must be converted to daily doses. This label also supports those programs that only compound PN formulations in liter quantities so that prescriptions may be written as quantity per liter and thus consistent with the additive as it appears on the label.

Finally, grams per total volume, with use of a 24-hour nutrient infusion system is most consistent with that of a nutrient label, requiring the least number of calculations to determine the calorie or gram dose per day. It also supports the most cost-effective system of PN compounding and delivery, which is the 24-hour nutrient infusion system. This system has been determined to decrease PN wastage and to reduce personnel time in compounding and administering PN. Conceptually, this system is successful when acute electrolyte disorders are managed separately from the PN, until the time that electrolyte changes in the PN go into effect. This system also requires the use of automated compounding devices, which have been shown to be more accurate and faster than gravity-fill PN admixture systems.

**PN LABEL TEMPLATE**

The sample PN label templates provide a format to standardize labels for adult, pediatric and neonatal patients. A supplemental label template for IVFE is also provided for those instances when IVFEs are administered separate from the PN admixture. Due to the complex nature of the label, there are several points that should be clarified:
- The amount per day is the only column required on the adult label, but some programs accustomed to amounts per liter may supplement the label by adding a second column reflecting quantity per liter in parenthesis. The components are labeled as amount per day to facilitate review of the order for appropriate nutrient doses. However, certain additives expressed as quantity per liter in parenthesis on the PN label template, may be useful to the clinician in determining whether the PN may be infused via peripheral or central vein. It is also useful to the pharmacist in determining electrolyte compatibility since these are reported by concentration rather than amount. Those familiar with ordering PN electrolytes (similar to other intravenous fluids) as mEq/L, will be able to interpret the mEq/L electrolyte content easier if provided in this format on the PN label. Finally, many programs order additives as quantity/liter. Labeling as such allows for the final check of the PN by the nurse versus the physician’s order, prior to its administration. This final check to confirm that the PN content is the same as the physician’s order is an essential component of the PN system. In the neonatal and pediatric patient, it is common to order PN components in amount/kg. Therefore, the PN label for these patients shall also express components as amount/kg/day, in addition to amount/day. The label can be further supplemented by an additional column expressing components as amount/liter or amount/100 ml in parenthesis, for those who are accustomed to ordering in this format. Care should be taken in developing a label that is clear and concise and of a size that fits neatly on the PN admixture. Accordingly, some may choose to dispense the PN with a supplemental form providing these optional details that may also be used for documenting PN administration in the patient’s chart.
- The PN label specifies the route of administration.
- The administration date and time and beyond-use date and time are expressed clearly on the label. The administration date and time, as the term denotes, is the date and time the PN is scheduled to be administered to the patient. This may be the same day that it was compounded and is different from the date and time of admixture, which should be included on the compounding worksheet but is not necessary on the label.
- The dosing weight is provided so that anyone evaluating the contents of the label may determine if the doses of nutrients are appropriate. Dosing weight refers to the weight used in calculating nutrient doses.
- The inorganic phosphorus content is provided as both
## Standard PN Label Template

### Adult Patient

<table>
<thead>
<tr>
<th>Institution/Pharmacy Name, Address and Pharmacy Phone number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Administration Date/Time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Base Formula</th>
<th>Amount/day</th>
<th>(Amount/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose</td>
<td>g</td>
<td>(g/L)</td>
</tr>
<tr>
<td>Amino acids&lt;sup&gt;a&lt;/sup&gt;</td>
<td>g</td>
<td>(g/L)</td>
</tr>
<tr>
<td>IVFE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>g</td>
<td>(g/L)</td>
</tr>
</tbody>
</table>

### Electrolytes

| Sodium chloride | mEq | (mEq/L) |
| Sodium acetate | mEq | (mEq/L) |
| Sodium phosphate | mmol of P | (mmol/L) |
| Potassium chloride | mEq | (mEq/L) |
| Potassium acetate | mEq | (mEq/L) |
| Potassium phosphate | mmol of P | (mmol/L) |
| Calcium gluconate | mEq | (mEq/L) |
| Magnesium sulfate | mEq | (mEq/L) |

### Vitamins, trace elements and medications

| Multiple vitamins<sup>a</sup> | mL |
| Multiple trace elements<sup>a</sup> | mL |
| Insulin | Units | (Units/L) |
| H₂ - antagonists<sup>a</sup> | mg |

Rate _____ mL/hour  
Volume _____ mL  
Infuse over ____ hours

Formulation contains _____ mL plus _____ mL overfill  
Discard any unused volume after 24 hours

***Central Line Use Only***

<sup>a</sup> Specify product name.

<sup>g</sup> = gram.

---

- the mmol quantity of phosphorus as well as the mEq quantity of the additive salt’s cation; potassium or sodium.
- If the PN formulation includes overfill, it is clearly stated on the label.
- Rate is expressed in mL/hour over 24 hours. If the PN formulation is cycled, the infusion duration and rates are to be expressed on the label.
- For home care, additives to be admixed at home are labeled as Patient Additives.
An auxiliary label may also be desired that would list the individual electrolytes as mEq, and the phosphorus content as mmol provided per day. The auxiliary label could also express the total calories provided per day, as well as the percent of total calories provided by carbohydrate and fat.

Notation of who prepared and checked the PN formulation is not required on the label if this is done on a compounding worksheet maintained in the pharmacy.

If IVFE are not included in the PN formulation, this line may be omitted from the label.

**PRACTICE GUIDELINES**

1. The labels for PN formulations shall be standardized and include:
   - The amount per day is the only column required

---

### Standard PN Label Template

**Neonate or Pediatric Patient**

<table>
<thead>
<tr>
<th>Institution/Pharmacy Name, Address and Pharmacy Phone number</th>
<th>Name</th>
<th>Dosing Weight</th>
<th>Location</th>
<th>Administration Date/Time</th>
<th>Do Not Use After: Date/time</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Base Formula</th>
<th>Amount/kg/day</th>
<th>Amount/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dextrose</strong></td>
<td>g/kg</td>
<td>g</td>
</tr>
<tr>
<td><strong>Amino acids</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>g/kg</td>
<td>g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Amount/kg/day</th>
<th>Amount/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium chloride</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Sodium acetate</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Potassium chloride</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Potassium acetate</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Potassium phosphate</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Sodium phosphate</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mEq/kg</td>
<td>mEq</td>
</tr>
<tr>
<td><strong>Calcium gluconate</strong></td>
<td>mL/kg</td>
<td>mL</td>
</tr>
<tr>
<td><strong>Magnesium sulfate</strong></td>
<td>mL/kg</td>
<td>mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamins, trace elements and medications</th>
<th>Amount/kg/day</th>
<th>Amount/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple vitamins</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mL/kg</td>
<td>mL</td>
</tr>
<tr>
<td><strong>Multiple trace elements</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mL/kg</td>
<td>mL</td>
</tr>
<tr>
<td><strong>L-cysteine</strong></td>
<td>mg/kg</td>
<td>mg</td>
</tr>
<tr>
<td><strong>H₂ antagonists</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mg/kg</td>
<td>mg</td>
</tr>
<tr>
<td><strong>L-Carnitine</strong></td>
<td>mg/kg</td>
<td>mg</td>
</tr>
</tbody>
</table>

Rate ____ mL/hour  Volume ______ mL  Infuse over 24 hours  
Admixture contains ______ mL plus ______ mL overfill

***Central Line Use Only***

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<sup>a</sup> Specify product name.

<sup>b</sup> Since the admixture usually contains multiple sources of sodium, potassium, chloride, acetate, and phosphorus, the amount of each electrolyte/kg provided by the PN admixture is determined by adding the amount of electrolyte provided by each salt.
on the label for the base formula, electrolyte additives, micronutrients and medications. This supports the use of the 24-hour nutrient infusion system.

- Using the quantity per liter option in parenthesis supports those programs that continue to admix PN in 1 liter volumes.
- The dosing weight is required on the label.

2. Auxillary labels or information may be used.

3. Patient transfer between healthcare environments requires pharmacist-to-pharmacist communication and documentation to insure the accurate transfer of the PN prescription.

4. The PN label is compared with the PN order and for beyond-use date before administration.

Special Considerations

The concepts used in developing the practice guidelines were developed for hospitalized patients and for institutions and organizations having a relatively large number of patients receiving PN therapy. It is assumed that these concepts apply to alternative health care settings, as well as those hospitals with only a few patients receiving PN. It may be that the cost of implementing a once-per-day nutrient infusion system that includes automated compounding would be excessive for pharmacies with small numbers of patients receiving PN. Various alternatives to achieving the concepts for labeling in these circumstances may be successful, but have yet to be determined objectively.

REFERENCES

NUTRIENT REQUIREMENTS: ADULTS

General guidelines for protein, calorie, and fluid requirements in adult patients are provided in Table I. A dosing weight shall be determined for each patient. Various methods for adjusting the body weight of obese patients have been suggested, but none have been clearly validated. Assessment of energy expenditure in obese patients can be problematic. Indirect calorimetry may be required to improve the accuracy of energy requirement estimations, due to limitations of predictive equations in obese patients.

Protein requirements have been estimated based on metabolic demand. Restriction of protein is seldom required in patients with renal or hepatic disease. In patients receiving renal replacement therapy, protein may need to be supplemented. In patients with liver disease, protein restriction should be implemented for the acute management of overt hepatic encephalopathy only when other treatment modalities have failed. Protein restriction is not indicated in the management of chronic hepatic disease.

The standard distribution of nonprotein calories is 70–85% as carbohydrate and 15–30% as fat. This distribution may be adjusted based on tolerance; however, there is limited clinical benefit when fat content exceeds 30% of nonprotein calories. Further methods to estimate dosing are based on body weight. In adult patients, it is recommended that the fat content of the PN formulation not exceed 2.5 g/kg/day and carbohydrate content not exceed 7 g/kg/day.

Although rare in recent years, essential fatty acid deficiency (EFAD) may still occur in the contemporary period of specialized nutrition support. Failure to provide at least 2% to 4% of the total caloric intake as linoleic acid and 0.25% to 0.5% of total caloric intake as alpha linolenic acid may lead to a deficiency of these two essential fatty acids. Manifestations of this syndrome can include alterations in platelet function, hair loss, poor wound healing, and dry, scaly skin unresponsive to water miscible creams. The time in which EFAD may develop during administration of fat-free PN is variable, based upon the underlying nutritional status, disease state, and age of the patient. In general, the majority of hospitalized adults who receive no dietary fat, develop biochemical evidence of EFAD after 4 weeks of fat-free PN. Hypocaloric feeding may provide some protection against development of EFAD while receiving fat-free PN. This is presumed to be secondary to the liberalization of essential fatty acids (EFAs) from endogenous fat stores into the circulation. Although 2 weeks of a high-protein, hypocaloric fat-free PN regimen has been shown to maintain plasma linoleic acid levels in postsurgical patients, clinical signs of EFAD have been detected in obese patients who received no exogenous EFAs for 20 days. Studies of patients receiving home PN have shown that biochemical evidence of EFAD syndrome may develop after several months of not receiving IVFE. The amount of fat taken by mouth and the efficiency of absorption were identified as factors influencing the need for the continued provision of IVFE. In determining the adequacy of EFA provision, it is important to recognize the varying EFA content of various IVFE sources. For example, commercially available IVFE in the United States contain approximately 55–60% of total calories as linoleic acid and 3–4% of total calories as alpha linolenic acid. Structured lipid products available in Europe contain significantly lower proportions of EFAs, owing to the substitution of long-chain EFAs by medium-chain fatty acids. Topical EFA application has been shown to be effective in preventing EFAD in some patients but it has demonstrated poor efficacy when used to treat an already existing EFAD.

Standard ranges for parenteral electrolytes assume normal organ function and normal losses (Table II). Sodium and potassium requirements for a given patient are highly variable and generally not limited by compatibility restraints; however, large quantities of these cations may destabilize IVFE. In general, sodium and potassium requirements in the PN formulation are 1–2 mEq/kg/day, but should be customized to meet individual patient needs. Restrictions of potassium, phosphate, or magnesium may be required in patients with renal disease due to impaired excretion. Conversely, requirements of these electrolytes may be increased due to excessive losses, intracellular shifts, or increased metabolic demands. As discussed in section VI, the parenteral supplementation of phosphate, magnesium, and calcium in the PN formulation is limited by physical compatibility. Some commercially available amino acid injection products contain phosphorus, the content of which shall also be considered in determining compatibility. Chloride and acetate content should be adjusted to maintain acid-base balance. In general, acid-base balance can be maintained by using approximately equal amounts of chloride and acetate, but may require adjustment based on the clinical situation. Amino acid solutions themselves contain various amounts of chloride and acetate, depending on the individual product, for buffering purposes. For

| Table I: Daily protein & caloric requirements for the adult
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
</tr>
<tr>
<td>Catabolic patients</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>(renal replacement therapy)</td>
</tr>
<tr>
<td>Acute renal failure + catabolic</td>
</tr>
<tr>
<td>Energy</td>
</tr>
<tr>
<td>Fluid</td>
</tr>
</tbody>
</table>

| Table II: Daily electrolyte additions to adult PN formulations* |
| Electrolyte | Standard Requirement |
| Calcium | 10–15 mEq |
| Magnesium | 8–20 mEq |
| Phosphorus | 20–40 mmol |
| Sodium | 1–2 mEq/kg |
| Potassium | 1–2 mEq/kg |
| Acetate | As needed to maintain acid-base balance |
| Chloride | As needed to maintain acid-base balance |

*Standard intake ranges based on generally healthy people with normal losses.
and folic acid as well as addition of vitamin K are based on the recommendations from a 1985 workshop sponsored jointly by the American Medical Association’s (AMA) Division of Personal and Public Health Policy and FDA’s Division of Metabolic and Endocrine Drug Products. Specific modifications of the previous formulation include increasing the provision of ascorbic acid (vitamin C) from 100 mg/day to 200 mg/day, pyridoxine (vitamin B₆) from 4 mg/day to 6 mg/day, thiamin (vitamin B₁) from 3 mg/day to 6 mg/day, folic acid from 400 mcg/day to 600 mcg/day, and addition of phylloquinone (vitamin K) 150 mcg/day (Table III). When using the 12-vitamin formulation, vitamin K can be given individually as a daily dose (0.5–1 mg/d) or a weekly dose (5–10 mg one time per week). Patients who are to receive the anticoagulant warfarin should be monitored more closely when receiving vitamin K to assure the appropriate level of anticoagulation is maintained. It is reasonable to supplement the PN with thiamin (25–50 mg/d) in PN patients who have a history of alcohol abuse, especially when they did not receive thiamin at hospital admission, or in times of parenteral vitamin shortages (common in the U.S. in the 1990s). The United States has been plagued with two periods of short supply of parenteral vitamin products in the 1990s. This has resulted in vitamin deficiencies in patients receiving PN without parenteral vitamins. Several recommendations emanated from A.S.P.E.N. following the latest parenteral vitamin shortage: (1) use oral vitamins when possible, especially liquid vitamins of defined content via feeding tubes, (2) restrict the use of vitamin products in PN during periods of short supply, such as one infusion three times per week, (3) administer thiamin, ascorbic acid, niacin, pyridoxine, and folic acid daily as individual entities in the PN during periods of short supply, (4) administer vitamin B₁₂ at least once per month during periods of short supply.

Guidelines for parenteral trace element requirements in adults are provided in Table IV.¹⁴,¹⁵ The guidelines should be considered approximations, and it should be recognized that variations among individual patients may exist. Reductions in manganese and copper dosing should be considered in patients with hepatobiliary disease due to impaired excretion. In addition, many of the components of the PN formulation have been shown to be contaminated with trace elements such as zinc, copper, manganese, chromium, selenium, and aluminum.¹⁶ Therefore, patients receiving long-term use of PN therapy are at risk of trace element toxicity and serum monitoring is necessary.

Iron is not routinely recommended in patients receiving PN therapy and is not a component of current injectable multiple trace element preparations.¹⁷ Parenteral supplementation of iron should be limited to conditions of iron deficiency when the oral route is ineffective or not tolerated. In patients with iron deficiency anemia, therapeutic (replacement) doses of iron may be estimated based on weight and hemoglobin concentration. Provision of maintenance iron therapy is generally not required but has been used in patients receiving long-term PN. In the absence of blood loss, a parenteral iron dose of 25 to 50 mg once monthly is estimated to meet maintenance requirements. However, it is important to monitor iron status on a routine basis (e.g., serum ferritin every 1–3 months) whenever providing ongoing doses of iron in order to minimize the risk of iron overload. Iron dextran has been added to nonIVFE-containing PN formulations, but requires caution due to compatibility limitations. It shall not be added to TNA because it can destabilize the IVFE and result in the formation of large oil droplets that may be harmful if infused (see compatibility section). Iron sucrose and sodium ferric gluconate provide therapeutic options for the parenteral supplementation of iron, but compatibility data with PN formulations is not available.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Daily requirements for adult parenteral vitamins*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin</td>
<td>Requirement</td>
</tr>
<tr>
<td>Thiamin (B₁)</td>
<td>6 mg</td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>Niacin (B₃)</td>
<td>40 mg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>600 mcg</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>15 mg</td>
</tr>
<tr>
<td>Pyridoxine (B₆)</td>
<td>6 mg</td>
</tr>
<tr>
<td>Cyanocobalamin (B₁₂)</td>
<td>5 mcg</td>
</tr>
<tr>
<td>Biotin</td>
<td>60 mcg</td>
</tr>
<tr>
<td>Ascorbic Acid (C)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>3300 IU</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>200 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10 IU</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>150 mcg</td>
</tr>
</tbody>
</table>

*FDA requirements for marketing an effective adult parenteral vitamin product.¹³

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Daily trace element supplementation to adult PN formulations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace Element</td>
<td>Standard Intake¹⁴,¹⁵</td>
</tr>
<tr>
<td>Chromium</td>
<td>10–15 mcg</td>
</tr>
<tr>
<td>Copper</td>
<td>0.3–0.5 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>Not routinely added</td>
</tr>
<tr>
<td>Manganese</td>
<td>60–100 mcg†</td>
</tr>
<tr>
<td>Selenium</td>
<td>20–60 mcg</td>
</tr>
<tr>
<td>Zinc</td>
<td>2.5–5 mg</td>
</tr>
</tbody>
</table>

*Standard intake ranges based on generally healthy people with normal losses.
†The contamination level in various components of the PN formulation can significantly contribute to total intake. Serum concentrations should be monitored with long-term use.
NUTRIENT REQUIREMENTS: PEDIATRICS

Standard nutrient ranges for infants and children receiving PN have been established. Rapidly changing organ function, metabolic immaturity, and normal but rapid weight gain, particularly in neonates and infants, result in age-related descriptors of nutrient need. Therefore, each table characterizes ranges for neonates, infants, children, and adolescents (Tables V through X). As can be readily appreciated, requirements for fluids, protein, and energy are substantially higher on a unit-of-weight basis for children than for adults. Careful monitoring of growth is necessary, as a component of assessing adequacy of nutrient provision. Above 18 years of age, estimated nutritional requirements should be established using nutrient ranges suggested for the adult population.

Protein restriction in certain disease states such as hepatic and renal failure should be done with caution and in consideration of the need for adequate protein to support growth in the pediatric population. Additionally, protein losses during dialysis need to be considered and appropriately replaced. Manufacturers of neonatal/infant amino acid formulations recommend the addition of L-cysteine hydrochloride to the 2-in-1 PN formulation just prior to administration. A commonly recommended dose is 40 mg L-cysteine hydrochloride per gram of amino acids. Current practice suggests supplementation with L-cysteine hydrochloride for the first year of life, although practice varies widely. Addition of L-cysteine hydrochloride to the PN formulation reduces the pH, thereby improving calcium and phosphorus solubility. It has also been shown to normalize plasma taurine levels.

The distribution of PN nonprotein calories for pediatric patients does not vary significantly from that for the adult receiving PN; however, it is worth noting that the typical enteral diet of the neonate or infant derives approximately 50% of nonprotein calories from fat. Therefore, a PN formulation appears less physiologically similar to standard enteral feedings in the neonate or infant than in the older child and adult. There is evidence that the 20% IVFE is preferable to the 10% product, especially for use in neonates and infants. In addition to its greater caloric content per unit volume, the lower content of surface active agents (egg phosphatides) per gram of fat results in more normal concentrations of components of circulating lipoproteins, especially low density lipoproteins. In the very low birth weight infant, the use of the 20% IVFE does require accurate and low flow pump delivery systems. In general, 3 g/kg/day is the accepted limit for IVFE administration in the small for gestational age neonates and preterm neonates less than 32 weeks gestational age. Concerns regarding EFAD are addressed in the adult section of nutrient requirements.

A limited endogenous store of fatty acids in neonates and infants versus adults contribute to the discrepancy in time in which EFAD syndrome may occur. Neonates have been reported to develop biochemical signs of EFAD as early as the second day of life and up to 2 weeks after fat-free PN.

Standard ranges for electrolytes, vitamins, and trace elements for infants and children with normal organ function are provided in Tables VIII through X. Calcium and phosphorous requirements of the neonate and infant are substantially different from those of the older child and are dramatically different from the adult requirements (Table VIII). These differences in needs are reflected in the composition of neonatal and infant formulas and human milk. When one attempts to meet these increased requirements in pediatric PN formulations, problems can arise because of incompatibility of calcium and phosphate salts. In a child weighing more than 50 kg, adult electrolyte dosage guidelines should generally be used.

Guidelines for vitamin and trace element additions to PN solutions for pediatric patients up to age 11 have been published (Tables IX and X). Adult multivitamins should be used for a child who weighs more than 40 kg or is greater than 11 years of age. Like adults, the guidelines should be considered approximations of need, with individual patient variation to be expected. Alteration of trace element dosage may be required in cases of hepatic or renal dysfunction. The long-term use of multiple trace element products at recommended doses has been associated with excessive serum concentrations of chromium. The ratio of trace elements in commercially available pediatric multiple trace element products results in excessive intake of manganese if recommended doses of zinc are given. It is clear that micronutrient requirements for children receiving PN is a fertile area for research and an area in which further commercial product development is required. In general, the recommendations for the use of iron in pediatric PN are consistent with those pre-

### Table V

**Daily fluid requirements for pediatric patients**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1500 g</td>
<td>130–150 mL/kg</td>
</tr>
<tr>
<td>1500–2000 g</td>
<td>110–130 mL/kg</td>
</tr>
<tr>
<td>2–10 kg</td>
<td>100 mL/kg</td>
</tr>
<tr>
<td>&gt;10–20 kg</td>
<td>1000 mL for 10 kg + 50 mL/kg for each kg &gt;10</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1500 mL for 20 kg + 20 mL/kg for each kg &gt;20</td>
</tr>
</tbody>
</table>

*Assumes normal age-related organ function.

### Table VI

**Daily protein requirements (g/kg) for pediatric patients**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Protein requirement (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonates</td>
<td>3–4</td>
</tr>
<tr>
<td>Infants (1–12 months)</td>
<td>2–3</td>
</tr>
<tr>
<td>Children (&gt;10 kg or 1–10 yrs)</td>
<td>1–2</td>
</tr>
<tr>
<td>Adolescents (11–17 yrs)</td>
<td>0.8–1.5</td>
</tr>
</tbody>
</table>

### Table VII

**Daily energy requirements (total kcal/kg) for pediatric patients**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Energy requirement (kcal/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonate</td>
<td>90–120</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>85–105</td>
</tr>
<tr>
<td>6–12 months</td>
<td>80–100</td>
</tr>
<tr>
<td>1–7 yr</td>
<td>75–90</td>
</tr>
<tr>
<td>7–12 yr</td>
<td>50–75</td>
</tr>
<tr>
<td>&gt;12–18 yr</td>
<td>30–50</td>
</tr>
</tbody>
</table>
sented previously for adults. However, total iron needs can be dramatically lower in the pediatric patient, compared to adults. This necessitates vigilance, regarding the iron dose administered. The concentration of some parenteral iron preparations can result in life-threatening doses, even with the use of <1 mL of these commercial iron preparations.

Aluminum contamination. Since the late 1970s, evidence has been accumulating to show that small volume parenteral products, large volume parenteral products and pharmacy bulk packages used in compounding PN formulations are largely contaminated with aluminum. Contamination occurs primarily from the introduction of raw materials during the manufacturing process, with the aluminum-contaminated product sources of primary concern being calcium and phosphate salts, heparin, and albumin. Variable levels of contamination have also been noted with some trace element and vitamin products. Infants and children are extremely vulnerable to aluminum toxicity due to immature renal function and the likelihood for long-term PN. Alterations in bone formation, mineralization, parathyroid hormone secretion, and urinary calcium excretion have been attributed to aluminum toxicity in long-term PN patients or patients with renal impairment. Although they may not be receiving PN, thermal injury patients are at an increased risk for aluminum toxicity from the large quantities of human albumin and calcium gluconate they receive in the treatment of their burn injuries. The FDA recently mandated that manufacturers of products used in compounding PN shall measure the aluminum content of their products and disclose it on the label by July 2004. Large volume parenterals (i.e., amino acid solutions, concentrated dextrose solutions, IVFE and sterile water for injection) have a maximum limit of 25 mcg/L of aluminum. Small volume parenterals (i.e., electrolyte salts) and pharmacy bulk packages (i.e., parenteral multivitamins, trace element solutions) must be labeled with the maximum level of aluminum in the product at expiry. The FDA identified 5 mcg/kg/day as the maximum amount of aluminum that can be safely tolerated and amounts exceeding this limit may be associated with central nervous system or bone toxicity. The intent of the FDA ruling is to educate health care practitioners about aluminum exposure and facilitate the administration of low-aluminum parenteral solutions to patients in high-risk groups.

### PRACTICE GUIDELINES

1. Determination of protein, calorie, fluid, electrolyte, vitamin, and trace element components of a PN formulation should be based on standard nutrient requirements. The dose of each nutrient should fall within the accepted age-based standard range except when warranted by specific clinical situations.

2. IVFE in a dose sufficient to prevent EFAD should be provided to adult and pediatric patients who are NPO. Adults who fail to receive EFAs for 20 days are at risk for development of EFAD. In the absence of EFAs, children can develop EFAD over a shorter period of time, with neonates at risk of EFAD within 2 days of initiating lipid-free PN.

3. All patients receiving PN should receive a parenteral vitamin preparation on a daily basis.

4. Health care providers should choose PN components with the lowest aluminum content when possible to minimize parenteral aluminum exposure.

5. When the use of a commercially available multiple trace element combination product results in or

---

### TABLE VIII
**Daily electrolyte and mineral requirements for pediatric patients**

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Preterm neonates</th>
<th>Infants/children</th>
<th>Adolescents and children &gt; 50 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>2–5 mEq/kg</td>
<td>2–5 mEq/kg</td>
<td>1–2 mEq/kg</td>
</tr>
<tr>
<td>Potassium</td>
<td>2–4 mEq/kg</td>
<td>2–4 mEq/kg</td>
<td>1–2 mEq/kg</td>
</tr>
<tr>
<td>Calcium</td>
<td>2–4 mEq/kg</td>
<td>0.5–4 mEq/kg</td>
<td>10–20 mEq</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1–2 mmol/kg</td>
<td>0.5–2 mmol/kg</td>
<td>10–40 mmol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.3–0.5 mEq/kg</td>
<td>0.3–0.5 mEq/kg</td>
<td>10–30 mEq</td>
</tr>
<tr>
<td>Acetate</td>
<td>As needed to maintain acid-base balance</td>
<td>As needed to maintain acid-base balance</td>
<td>As needed to maintain acid-base balance</td>
</tr>
<tr>
<td>Chloride</td>
<td>As needed to maintain acid-base balance</td>
<td>As needed to maintain acid-base balance</td>
<td>As needed to maintain acid-base balance</td>
</tr>
</tbody>
</table>

*Assumes normal age-related organ function and normal losses.

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### TABLE IX
**Daily dose recommendations for pediatric multiple vitamins**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>AMA-NAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Dose (mL)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>1.5</td>
</tr>
<tr>
<td>1–3</td>
<td>3.25</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5</td>
</tr>
</tbody>
</table>

*Assumes normal age-related organ function.

†Pediatric multiple vitamin formulation (5 mL): A 2300 IU, D 400 IU, E 7 IU, K 200 mcg, C 80 mcg, B1 1.2 mg, B2 1.4 mg, B12 17 mg, B5 5 mg, B6 1 mg, B12 1 mcg, Biotin 20 mcg, Folic acid 140 mcg.

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### TABLE X
**Trace element daily requirements for pediatrics**

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Preterm neonates &lt;3 kg (mcg/kg/d)</th>
<th>Term neonates 3–10 kg (mcg/kg/d)</th>
<th>Children 10–40 kg (mcg/kg/d)</th>
<th>Adolescents &gt;40 kg (mcg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>400</td>
<td>50–250</td>
<td>50–125</td>
<td>2–5 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>20</td>
<td>5–20</td>
<td>200–500 mcg</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td>1</td>
<td>1</td>
<td>40–100 mcg</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>0.05–0.2</td>
<td>0.2</td>
<td>0.14–0.2</td>
<td>5–15 mcg</td>
</tr>
<tr>
<td>Selenium</td>
<td>1.5–2</td>
<td>2</td>
<td>1–2</td>
<td>40–60 mcg</td>
</tr>
</tbody>
</table>

*Assumes normal age-related organ function and normal losses.

†Recommended intakes of trace elements cannot be achieved through the use of a single pediatric multiple trace element product. Only through the use of individualized trace element products can recommended intakes of trace elements be achieved.
increases the risk of trace element toxicity or deficiency states, the use of individual trace element products is warranted.

6. Parenteral iron shall not be routinely supplemented in patients receiving PN therapy. It should be limited to conditions of iron deficiency when oral iron supplementation fails and followed closely in an ongoing monitoring plan.

Special Considerations

Further work is required to determine optimal parenteral trace element requirements in adult and pediatric patients and develop commercially available multiple trace element solutions that better meet these requirements. The use of currently available multiple trace element solutions may result in toxicity or deficiency of certain trace elements in some disease states. This problem may be compounded by trace element contamination, particularly aluminum, found in large volume parenterals and additives.

REFERENCES


SECTION V: STERILE COMPOUNDING OF PARENTERAL NUTRITION FORMULATIONS

SCREENING THE PN ORDER

Background

Serious disorders and death have been attributed to PN formulations having inappropriate nutrient compositions. Deficiencies of trace elements and EFAs have been reported in both pediatric and adult patient populations. 1, 2 The most dramatic, yet insidious, example of the dangers associated with the omission of micronutrients occurred during the 2 periods when there was a national parenteral vitamin shortage. 3, 4 At that time, omission of parenteral vitamins resulted in three deaths of patients predisposed to vitamin deficiencies. Specifically, a refractory lactic acidosis led to the death of three patients associated with thiamin deficiency.
that was accentuated by the administration of dextrose in the PN formulation. Similarly, a death related to the omission of dextrose from a neonatal PN caused irreversible brain damage. Finally, life-threatening deficiencies have resulted when patients received phosphate-free PN.\(^5\) Overdoses of nutrients included in PN may also be harmful. As explained in Section I, the incorrect admixture of PN resulting in excessive dextrose infusions led to a patient's death, and a 50-fold error in an iron dextran solution caused serious liver damage in a child. In all these cases, there was inadequate review of the PN prescription for appropriateness of dose and adequacy of nutrient composition. It is the responsibility of the pharmacist-by education, training, and experience to review each prescription for appropriate indication, dose, and route of administration, and the potential for drug-drug, drug-nutrient and drug-laboratory interactions.\(^6\) Patient information such as height, dosing weight, serum electrolyte and glucose values, hepatic and renal and gastrointestinal function should be available to assess the adequacy of the PN prescription.\(^7\)

For those systems requiring that the PN prescription be rewritten each day, the potential exists for transcription errors that omit or significantly increase nutrient doses. In this regard, it is important when refilling the day's order for PN therapy that the pharmacist review the contents of the PN for consistency with the previous day's prescription. Major deviations should be questioned, to avoid nutrition-related complications. For example, the pharmacist should clarify with the prescribing clinician a prescription for a patient if regular insulin was present in the previous day's order at a dose of 20 units and the present order is for 100 units without a change in the quantity of dextrose received between the two days. In this case, it is both professionally appropriate and clinically reasonable to question the order. Other orders that might be appropriately questioned are drug and nutrient quantities; other large-scale changes including omissions, dramatic increases, or decreases; and other types of extreme day-to-day fluctuations.

### PRACTICE GUIDELINES

1. The calorie, protein, fluid, electrolyte, vitamin, trace element and medication content is reviewed for each and every PN prescription to assure that a complete and balanced nutrient formulation is provided. Balanced is defined as the presence of the proper proportion of calories, protein, fluid, electrolytes, vitamins and trace elements, to assure adequate use by and assimilation into the body.

2. Each of the PN components should be assessed for appropriateness of dose and for the potential of a compatibility or stability problem.

3. Any dose of a nutrient outside a normal range, that is not explained by a specific patient condition or history, shall be questioned and clarified before the PN is compounded.

### Special Considerations

Traditionally, the pharmacist is assigned the responsibility of verifying the indication, dose, and use of a drug or nutrient, as is the case with PN. It is recognized that because of the variety in the organization of nutrition support teams, this responsibility may be reassigned to other team members in addition to the pharmacist. Also, some computer programs for PN admixture may be programmed to cue the pharmacist that the PN formulation is inappropriate when nutrient doses are outside an acceptable range.

### PN COMPOUNDING

#### Background

The 1994 FDA Safety Alert (referred to in Section I) highlights the serious consequences that are possible when quality-compounding practices are not in place. The responsibility of the dispensing pharmacist is to assure that the PN is prepared, labeled, controlled, stored, dispensed, and distributed properly.\(^7\) PN formulations are considered medium-risk sterile preparations because of the large number of chemical entities found in the admixture process and the complex nature of PN admixing, whether with gravimetric or automated compounding.\(^5\) Serious harm may come to patients receiving a PN formulation that has precipitates resulting from a chemical interaction between components that are present in an excessive dose, exposed to extremes of temperature, or admixed in an improper sequence. Automated or manual methods of PN compounding are available. The compounding of the PN formulation can be accomplished manually through the separate addition of nutrients via syringe and needle delivery or with the aid of sterile solution transfer sets. The manual method allows the pharmacist to decide the order of mixing and should be carefully undertaken to avoid potentially lethal incompatibilities. Alternatively, automated compounding devices are widely available that admix PN under computer-assisted commands connected to special hardware housed with sterile, disposable compounding sets. According to The American Society of Health System Pharmacists (ASHP) guidelines, the risk level of the compounding procedure for automated PN preparations is such that it is recommended that the pharmacist verify data entered into the compounding device prior to PN preparation; perform end-product checks to verify compounding accuracy and, periodically observe the operation of the device to assure it is working properly.\(^9\) Assistance in optimizing the compounding sequence for automated compounding devices should be obtained through consultation with the manufacturer of macronutrients currently used at the institution as well as the manufacturer of the compounding device because brand-specific issues might influence compatibility of the final formulation. PN products pre-mixed by the manufacturer are available in a variety of forms that include, for example, crystalline amino acids with electrolytes, amino acids/dextrose kits as either separate entities or in the same container separated by a divider that can be released or activated to
produce the final admixture. However, even these pre-
assembled units of use packaging may require some
level of pharmaceutical compounding in an aseptic
environment prior to use.

Professional organizations have published guide-
lines for compounding and dispensing sterile products.
ASHP had published guidelines\(^{10}\) in 2000 on quality
assurance for pharmacy-prepared sterile products,
while the United States Pharmacopeia (USP) recently
published the official compendium *The United States
Pharmacopeia and The National Formulary*, which
includes a chapter on pharmaceutical compounding of
sterile preparations in 2003.\(^{8}\) Sterile products are
divided into three levels of risk based upon the proba-
bility of exposing multiple patients to microbial con-
taminants (microorganisms, spores, endotoxins) and
physical contaminants (foreign chemicals and physical
matter). ASHP and the USP use slightly different ter-
minologies for the risk levels of microbial contamin-
ation for sterile products compounded within pharma-
cies. The ASHP guidelines utilize the risk-level
classification to the patient from least (level 1) to great-
est (level 3) potential based upon the danger of expos-
ing patients to inaccurate ingredients or pathogens. It
is also based upon microbial growth factors influenced
by product storage time, temperature and product abil-
ity to support microbial growth, surface and time expo-
sure of critical sites, and microbial bioload in the envi-
ronment. Drawing a sterile product into a sterile
syringe or transferring a sterile product from a vial
into a commercially produced intravenous bag is an
example of an ASHP risk level 1 (or a USP low-risk
process). Risk level 2 within the ASHP guidelines
applies to the automated compounding of PN formula-
tions due to the complex and numerous manipulations
of sterile ingredients obtained from licensed manufac-
turers into a sterile container by using closed-system
aseptic transfer. The newer USP compounded sterile
preparations (CSP) risk levels are designated as low,
medium, and high based upon the corresponding prob-
ability of contaminating a sterile preparation with
microbial and chemical/physical contamination. These
risk levels apply to the quality of CSP immediately
after the final aseptic mixing and were adopted as
required standards for pharmacies/pharmacists in the
United States. Compounding PN formulations is clas-
sified by USP as medium-risk level given the multiple
injections, detachments, and attachments of nutrient
source products to be delivered into a final sterile con-
tainer. If a non-sterile ingredient such as glutamine is
added to the PN formulation, the risk level increases to
high. According to the ASHP guidelines and USP stan-
dards, all compounded sterile preparations shall be
prepared in a class 100 environment, such as a certified
horizontal- or vertical-laminar-airflow workbench. Per-
sonnel are required to wear clean gowns or cover-alls,
as scrub attire by itself is not acceptable. Gloves,
masks, hair covers, shoe covers and removal of hand,
finger and wrist jewelry are recommended during the
compounding process. Mishandling of these prepara-
tions has resulted in reports of septic morbidity and
even death due to extrinsic contamination.

<table>
<thead>
<tr>
<th>USP risk level</th>
<th>Controlled room temperature</th>
<th>2°–8°C</th>
<th>≤–20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤48 hours</td>
<td>≤14 days</td>
<td>≤45 days</td>
</tr>
<tr>
<td>Medium*</td>
<td>≤30 hours</td>
<td>≤7 days</td>
<td>≤45 days</td>
</tr>
<tr>
<td>High</td>
<td>≤24 hours</td>
<td>≤3 days</td>
<td>≤45 days</td>
</tr>
</tbody>
</table>

*Level assigned to PN formulation compounding from USP Chapter 797.

There are two critical factors in establishing beyond-
use dating (currently designated as “do not use after”
dating) for a PN formulation, namely microbial steril-
ity and chemical stability. Unfortunately, microbial
sterility testing of batch-prepared PN formulations
rarely occurs in most pharmacies. If sterility testing
within the pharmacy is not performed for a PN for-
mulation and literature sources are unavailable support-
ing beyond-use dating, then the beyond-use dating of
the preparation cannot exceed the published limits by
the USP (Table 1). Chemical stability is defined as a
PN formulation maintaining its labeled strength
within 10% until its beyond-use date and is rarely
based on preparation-specific chemical assay results.
Exposure temperatures during storage and use, char-
acteristics of the sterile container used (e.g., multi-
layer bags), and hydrolysis or oxidation of ingredients
are only a few of the time-dependent factors used to
establish chemical stability.

Observing the physical appearance of the final PN
formulation is one of the most fundamental quality
assurance measures that pharmacists routinely apply.
Although it represents a crude measure of compatibil-
ity, it does identify gross particulate matter that likely
represents the greatest clinical risk of embolic events if
infused into the patient. The process generally includes
a detailed assessment of the final formulation against
a dark background under high-intensity illumination.
For translucent intravenous solutions, the highly
trained eye is searching for the presence of insoluble
particulate matter, such as ‘cores’ from elastomeric vial
enclosures, cotton fibers from alcohol wipes, as well as
characteristic indicators of an incompatible formula-
tion such as gas formation, turbidity or haziness, and
crystal formation. It is important to remember that in
the absence of any obvious physical signs of incompat-
ibility, visual clarity does not equate with safety. Sub-
visible particulate matter may exist and are capable of
inducing an embolic event that originates at the level
of the capillaries. However, visual assessments are
valuable and necessary in the routine quality assur-
ance process, but they should be supplemented with
other safety-enhancing measures that include suffi-
cient documentation of the concentrations of nutrients
prepared, use of filters in the manufacturing process or
during the infusion, and possibly particle-size analysis
when available. Documentation of the daily compounding
activities for PN, irrespective of the products or
procedures used, should include batch records for all
formulations prepared that are consistent with insti-
tutional policies and procedures.

For opaque parenteral dispersions such as TNAs,
visual assessments can still be performed. The princi-
pical aim of these assessments is focused on signs of phase separation, in which the unstable emulsion is manifested by the presence of free oil either as individually discernible fat droplets or a continuous layer at the surface of the formulation. In general, light creaming is a common occurrence and not a significant determinant of infusion safety except in extreme cases.

**PRACTICE GUIDELINES**

1. The additive sequence in compounding shall be optimized and validated as a safe and efficacious method.
2. If the manual method currently in use at an institution has not been recently reviewed, or if the contract with a particular manufacturer of macro-nutrients is about to change, then a review of the compounding method is strongly recommended. This review shall include an evaluation of the most current literature as well as consultation with the manufacturer when necessary.
3. Manufacturers of automated methods of PN compounding shall provide an additive sequence that ensures the safety of the compounding device. This compounding sequence should be reviewed with the manufacturer of the parenteral nutrient products used by the institution. As most institutions in the U.S. are represented by buying groups with many participants, such buying groups should not only ensure the safety and support of the automated compounding device, but should avoid splitting PN contracts (mixing brands of amino acids, dextrose and IVFE) unless such combinations have adequate physicochemical data that ensures the stability, compatibility and safety of the final formulations commensurate with the data for single source PN products.
4. Each PN formulation compounded should be visually inspected for signs of gross particulate contamination, particulate formation and/or phase separation of TNAs.

**QUALITY ASSURANCE OF THE COMPOUNDING PROCESS**

**Background**

Numerous cases have been reported of adverse events associated with erroneous final concentrations of dextrose in parenteral fluids. Also, infectious events have occurred from microbial contamination of pharmacy-prepared PN formulations. In-process or end-product testing of PN should be performed in accordance with USP standards and ASHP guidelines for sterile product admixture.

Because of the complex nature of PN formulations, these processes may be modified to accommodate the special physicochemical characteristics of PN with use of the methodologies for gravimetric, chemical, or refractometric analysis and in-process testing.

**Gravimetric Analysis**

Weight-based delivery of PN additives is the principal method by which automated compounders prepare PN formulations. These devices provide a high degree of accuracy and accomplish it in a fraction of the time it takes with use of manual, gravity-fed compounding techniques. In general, as a final check, the PN formulation is weighed and is expected to be within an acceptable margin of error. However, while some automated compounding devices evaluate only the weight of the total contents, other compounding devices weigh the final admixture as well as individual additives. To ensure that certain additives having a narrow margin of safety are assessed individually, pharmacists can apply gravimetric techniques similar to those used by the compounding device. This is particularly important for additives such as potassium chloride and highly interactive salts such as phosphates. In the case of potassium chloride, a 2000-mL final PN volume with a 5% compounding error acceptance means that a 100-mL overfill would be tolerated. If the entire overfill came from the potassium chloride container(s), it could be lethal. Thus individual monitoring of certain PN additives is recommended, and this monitoring can be simply accomplished within the sterile compounding facility each day. The gravimetric method is preferred, with use of the analytical balance associated with the automated compounder.

**Chemical Analysis**

A random, but continuously applied assessment of the final dextrose concentration is reasonable. One approach is through the use of glucose measuring devices that allow for direct assessment of the dextrose concentration. Although these instruments have a limited effective range of detection, appropriate dilutions may be made from a PN aliquot to measure the final concentrations of dextrose and to assure that they are in accordance with the prescribed quantities intended for the patient. When this quality assurance method is devised, it is important to outline a stepwise procedure, validate the findings against appropriate control dextrose solutions, and apply the appropriate error analysis that gauges an acceptable margin of error.

**Refractometric Analysis**

Refractometers have been used in pharmacy practice for determining dextrose content. However, they may require training and experience in order to obtain consistent and reliable results. In addition, because refractometry measures a physical characteristic of dextrose (e.g., refractive index), it is an indirect determinant of dextrose concentration and is subject to interference by other components, as well as to variation in technique from one operator to another and in subsequent interpretation of the final results. As with direct measurement techniques of dextrose concentration, the procedures should be validated in a similar manner to assure the integrity of the results. Refractometers are rendered inoperable with TNAs, and therefore are of no use for these formulations.

**In-Process Testing**

There are three ways to test the integrity of the sterile compounding process of PN formulations, and
all three can be accomplished at any time before, during, or after the hours of operation for PN preparation. For purposes of this summary, ‘in-process’ can include any one of the aforementioned periods. The amount of potassium chloride used after each stock bottle exchange, along with the appropriate density conversion for the additive tested, can be determined gravimetrically at multiple points during the day, within the compounding facility. As long as the number of patients who received a portion of the stock from a container is properly recorded, the pharmacist can determine whether the delivery is accurate by analyzing a subset of the PN formulations and can take appropriate action for only those formulations affected, thereby reducing the costs associated with waste if they need to be remade. Similarly, individual PN containers can be analyzed for dextrose content during chemical or refractometric analysis, which can be applied in a cost-effective manner.

In addition to these assessments of hardware function, the software can be similarly challenged to see whether the response is appropriate to the command. For example, if an extraordinary amount of calcium and phosphorus are entered into the compounding program, does the software recognize a potential incompatibility? However, such challenges to the software program are best performed either before or after PN admixture, rather than during the time of operation. Such tests run the risk of an inadvertent compounding command that may be overlooked and could result in dispensing an incompatible and potentially dangerous formulation.

Process validation of aseptic procedures is recommended for PN formulations. Individuals involved in PN compounding should successfully complete a process validation of aseptic technique prior to being allowed to admix PN. Process simulation of the PN formulation may also be used but is more difficult since the PN formulation itself may limit or inhibit microbial growth if inadvertently contaminated during the compounding process.

### Practice Guidelines

1. Gravimetric analyses that indirectly assess the accuracy of the individual additives delivered or the final contents of the PN can be readily applied in the pharmacy practice setting. Particular attention should be focused on the most dangerous additives that tolerate the least margin of error, such as the potassium salts.
2. Chemical analyses that directly measure the final content of the individual additives can be incorporated into the PN compounding operations of the pharmacy. The accuracy of the PN dextrose content is an example of an additive that may be associated with significant morbidity and mortality.
3. Refractometric analysis is an alternative, as well as an indirect measure of the final additive concentration. For example, dextrose concentration is frequently assessed by this technique. However, this method is limited to PN formulations that do not contain IVFE.
4. In-process or end-product testing of PN formulations is recommended daily so as to assure a safe, final formulation is dispensed to the patient.
5. End-product testing of PN formulations prepared with automated compounding devices is recommended to verify compounding accuracy.
6. The aseptic sterile preparation of intravenous admixtures intended for patient administration should adhere to the USP (797) Pharmaceutical Compounding—Sterile Preparations Chapter and the ASHP Guideline on Quality Assurance for Pharmacy-Prepared Sterile Products.

### Special Considerations

Use of dual-chamber bags for PN formulations resolve the long-term stability issues of TNA especially for home PN patients. However, aseptic technique issues related to IVFE transfer from the original container to the dual chamber compartment may be similar to those for transfer to syringe as discussed in the PN administration section. This is not known and a process should be in place to assure sterile admixture, storage and administration of the IVFE component of the dual-chamber bag.

### References


### Section VI. Stability and Compatibility of Parenteral Nutrition Formulations

#### PN Stability

**Background**

The stability of PN formulations principally focuses on the degradation of nutritional components over
time. The Maillard reaction (‘the browning reaction’) is well-known and involves the complexation of carbohydrates by certain amino acids such as lysine, which is facilitated by temperatures used for sterilization of commercial products. Thus the combination of amino acids and dextrose is usually prepared in the pharmacy with stability of the final formulation determined by its storage conditions prior to administration. It is generally recognized that the sterile compounding of any PN accelerates the rate of physicochemical destabilization. Presently, certain amino acids, vitamins and IVFE are most susceptible to instability. Except for an isolated case report, the discoloration of commercial amino acid products forming a bluish hue is not associated with adverse effects. However, the oxidation reaction involving tryptophan that produces the discoloration should be prevented by storage away from light and, preferably, keeping the manufacturer’s protective packaging intact until the time of use.

From a clinical perspective, the physicochemical stability of PN formulations is largely focused on vitamins, several of which are known to deteriorate substantially over time and in the presence of oxygen. For the most part, despite their degradation, very few produce clinically significant disturbances in the acute care setting. They tend to be more important in patients with marginal body stores and who are dependent on long-term PN support. The clearest example of this was demonstrated in a case report of a home PN patient who received weekly batches of PN prepared by a hospital pharmacy in which the vitamins were added for a period of up to 7 days. Within 6 months, the patient had night blindness, was treated with a large intramuscular dose of vitamin A, and the symptoms resolved. Six months later, the patient had a relapse in symptoms, prompting an investigation into why the parenteral vitamin supplement was insufficient in meeting the patient’s needs. Because the vitamins were added up to a week before the solution was administered, substantial amounts of vitamin A were lost to degradation and adsorption into the plastic matrix of the infusion container. Adding the vitamins to the PN formulation daily just prior to infusion resolved the problem.

Similarly, when ascorbic acid was added in a batch fashion, it degraded and resulted in the formation of a large, discernible precipitate in the PN formulation. Careful analysis revealed that the precipitate was calcium oxalate. Oxalic acid is a degradation product of vitamin C that readily reacts with free calcium. Significant degradation can be avoided by adding vitamins just prior to infusion.

The sterile preparation of L-glutamine for addition to PN poses several concerns. L-glutamine has limited stability in PN formulations, and it requires specialized parenteral manufacturing techniques not routinely available in most institutional or home care pharmacies. The formulation needs to be evaluated to assure that its final contents meet the desired concentration and that it is sterile and free of pyrogens. Assuming the sterile compounding facility is qualified to make such a product, it is the pharmacist’s responsibility to quarantine the product and ensure that it passes the aforementioned tests prior to its infusion. In most cases, the quarantine period is at least 7 days in order to complete the microbiological analyses for the appearance of slow-growing pathogens. For products with limited stability, however, USP standards do allow for release of the product prior to the end of the quarantine period. Therefore, although less than ideal, quality control issues arising after quarantine can be dealt with retrospectively.

In addition to the above concerns for PN formulations, the stability of submicron lipid droplets shall also be maintained in TNA dispersions during the period of infusion. Because an anionic emulsifier stabilizes the TNA dispersion and numerous destabilizing cations (e.g., calcium, magnesium, sodium and potassium) are routinely included, the risk of infusing an unstable and potentially dangerous formulation is present. Generally, when producing a TNA, the manufacturer of the IVFE product clearly delineates its physicochemical limitations. The pharmacist is urged to use this brand-specific information and not extrapolate to other products.

The use of dual-chamber bags, whereby for example, the IVFE is physically separated from the remaining admixture components, can enhance the shelf life of TNAs. It’s greatest utility appears to be in the home-care setting where batch preparation of PN formulations is most common. Once all the nutrients from both chambers are combined for infusion, the new beyond-use date for completion of infusion should not exceed 24 hours and compatibility should be based on parameters for TNAs.

Although TNAs have been formulated for use in the neonate/infant, stability of lipid particles within the formulation shall be established for each combination of additives before use. The higher content of divalent cations (e.g. calcium and magnesium) can reduce particle zeta potential (negative surface charge), resulting in coalescence. Additionally, the higher content of calcium and phosphate in neonatal/infant PN formulations increases the risk of precipitation, which can go undetected because of TNA opacity.

### PN Compatibility

The complex formulations typical of PN pose several possible physicochemical incompatibilities. The most serious risk of incompatibility in PN formulations and thus the most imminent threat to the patient arises when macroprecipitates exceeding 5 microns develop in the formulation and pass into the central circulation. Two forms of precipitates (solid and liquid) may appear in the prepared formulation. Commonly, the existence of crystalline matter is most frequently cited in PN formulations, yet with the use of TNA, phase separation with the liberation of free oil constitutes the liquid precipitate.

Solid precipitates can develop when an incompatible combination of various salts is added to a PN formulation; this results in the formation of insoluble product. Calcium salts are one of the most reactive compounds and readily form insoluble products with a number of additives. Dibasic calcium phosphate (CaHPO₄) is an
example of one of the most dangerous incompatible combinations and has resulted in embolic deaths when infused in the clinical setting. This can be avoided through a variety of measures. First, calcium gluconate is the preferred form of calcium used in multi-component PN formulations. Calcium chloride is far more reactive than an equivalent amount of calcium gluconate salt. Therefore, solubility curves for calcium gluconate cannot be applied to calcium chloride. Second, the order of compounding is extremely important in order to avoid the formation of an insoluble precipitate that would otherwise be soluble if added in the correct sequence. Generally, phosphate should be added first, and calcium should be added near the end of the compounding sequence to take advantage of the maximum volume of the PN formulation. Other risks of forming solid precipitates include the use of bicarbonate salts when indicated to correct a base deficit through the PN. Again, bicarbonate reacts with calcium to form the insoluble product calcium carbonate. If an alkalinizing salt is indicated, then sodium or potassium acetate should be used. The dose of the alkalinizing salt is the same for either bicarbonate or acetate (1 mEq of bicarbonate has the same alkalinizing power as 1 mEq of acetate). Finally, ascorbic acid is a highly unstable vitamin that is sometimes added in supraphysiologic quantities (up to 2000 mg per day) in the PN for its antioxidant effects. However, because of its unstable characteristics, it readily degrades in the presence of oxygen to form oxalic acid, which is also highly reactive with calcium, forming the insoluble product calcium oxalate. Thus the use of this vitamin in supraphysiologic quantities should be given via separate infusion and not in the PN formulation.

Phase separation and the liberation of free oil from the destabilization of TNAs can result over time when an excess of cations is added to a given formulation. The higher the cation valence, the greater the destabilizing power; thus trivalent cations such as Fe$^{3+}$ (from iron dextran) are more disruptive than divalent cations such as calcium and magnesium. Monovalent cations such as sodium and potassium are least disruptive to the emulsifier, yet when given in sufficiently high concentrations, they may also produce instability. There is no safe concentration of iron dextran in any TNA. Of the divalent and monovalent cations, most adult patients’ clinical needs can be met without significant concern of producing an unstable and potentially dangerous formulation. Even the order of compounding can cause instability of TNAs, and the compounding sequence shall not place destabilizing additives such as the cations or hypertonic dextrose in close sequence with a minimally diluted IVFE. In general, the pharmacist should be guided by the instructions of the manufacturer for the macronutrients and the automated compounder in use to assure that all PN formulations are compounded optimally, and that they are safe and compatible.

The presence of enlarged lipid globules can be successfully identified if the proper techniques are used. There are only two stages of emulsion destabilization that are visually detectable by the naked eye, namely creaming and coalescence. As visual observation is the most routinely applied quality assurance method employed by practicing pharmacists, an appreciation of the physical signs of TNA integrity is essential. The initial stage in emulsion breakdown is creaming which occurs almost immediately upon standing once IVFE has been mixed with the other chemical constituents. The presence of a cream layer is visible at the surface of the emulsion as a translucent band separate from the remaining TNA dispersion, although the lipid particles in the cream layer are destabilized; their individual droplet identities are generally preserved. As such, this phase (creaming) of emulsion breakdown is still safe for patient administration.

The terminal stage of emulsion destabilization is the coalescence of small lipid particles forming large droplets that may vary in size from 5–50+ microns and pose potential clinical danger yet escapes visual detection. The existence of coalesced lipid particles in a TNA formulation is characterized by the variable presence of yellow-brown oil droplets at or near the TNA surface. In its usual presentation, the free oil may exist as individual spherical droplets or as segmented (discontinuous) oil layers. Careful observation of each TNA formulation is required to detect the subtle appearance of coalescence. In its most extreme form, the oil presents as a continuous layer of yellow-brown liquid at the surface of the formulation that is readily discernible from the remaining dispersion, and can be accompanied by marbling or streaking of the oil throughout the formulation. In either case, the presence of free oil in any form in a TNA should be considered unsafe for parenteral administration. The danger associated with the infusion of unstable lipid droplets enlarged through electromechanical destabilization is unclear. However, the existence of lipid globules 5 microns in diameter comprising 0.4% of the total fat present has been shown to be pharmaceutically unstable, and such formulations are considered unfit for intravenous administration.

Finally, standard PN formulations have been useful to organizations whereby the physicochemical stability and compatibility are assured via adequate documentation by the institution or the manufacturer of PN products. Such standardization limits the risk of compounding and dispensing potentially unstable or incompatible PN formulations. However, any change in the composition of standard formulations needs to be applied cautiously and with adequate assurance that the new or revised formulation is stable and compatible.

**Medication Administration with PN**

Since PN is infused intravenously, it is often considered as a vehicle for medication administration. Due to the complex nature of PN and potential for physicochemical interactions with drug-nutrient combinations, admixture of medications with PN is not advised. However, there are occasions when there is no other reasonable alternative. When this occurs, the predominant admixture issues that need to be resolved include the following:
• medication stability and compatibility with the PN or TNA is assured;
• evidence supports the clinical value of the medication administered in this manner.

Insulin use with PN. Insulin is commonly administered with PN. As noted in the Introduction, it is also associated with frequent harmful events. This is related to the variable methods used to control blood glucose levels in patients receiving PN. No one method of glucose control has been shown to be superior. Insulin requirements are generally higher and most variable during the first 24 hours of intensive care for critically ill patients. Strict serum glucose control at a value less than 110 mg/dL with a separate continuous insulin infusion has been shown to improve clinical outcomes (i.e. shorter ICU stay, ventilator use and mortality) in select surgical critically ill patients. Due to the potential for serious adverse events, insulin use in PN should be done in a consistent manner adhering to a defined protocol, in which healthcare personnel have adequate knowledge. One such approach can be summarized as follows:

Hyperglycemia and insulin resistance occur frequently in patients receiving PN. Diabetic patients receiving PN have been shown to have a 5-fold increase in catheter-related infections compared to nondiabetics. Clinical studies suggest that carbohydrate administration via PN greater than 4–5 mg/kg/min or greater than 20–25 kcal/kg/day exceeds the mean oxidation rate of glucose, giving rise to significant hyperglycemia, lipogenesis, and fatty liver infiltration. Although no clear consensus exists for the ideal level of glucose control in the hospitalized patient receiving PN, a reasonable target is a blood glucose level of 100 to 150 mg/dL.

Many approaches can be used to achieve appropriate glucose control in patients with diabetes or stress-induced hyperglycemia receiving PN. Patients should not receive more than 150 to 200 grams of dextrose on day 1 of PN. For patients previously treated with insulin, oral hypoglycemic agents, or patients with a fasting glucose concentration 200 mg/dL but in whom hyperglycemia is likely to occur, no more than 100 grams of dextrose per day should be administered. A basal amount of human regular insulin should also be added to the PN formulation to keep blood glucose concentrations less than 150 mg/dL in patients previously treated with insulin or oral hypoglycemic agents. (NOTE: only regular human insulin is compatible with PN formulations; other insulin products such as NPH, ultralente, lente, lispro, aspart, and glargine are NOT compatible with PN). A common initial regimen is 0.1 units of insulin per gram of dextrose in the PN infusion. If the patient is already hyperglycemic (>150 mg/dL), 0.15 units of insulin per gram of dextrose should be used. If the blood glucose is 300 mg/dL, PN should not be initiated until glycemic control is improved (<200 mg/dL). Obese patients with type 2 diabetes may require as much as 0.1 units of insulin for every 0.5 grams of dextrose whereas thin, type 1 diabetics may require only 0.1 units of insulin per 2 grams of dextrose. In general, the dextrose content of the PN should not be increased until glucose concentrations during the previous 24-hour period are consistently <200 mg/dL. If glucose is controlled with a specific insulin dose, the dose of insulin must be reassessed whenever the dextrose dose is modified.

Capillary glucose levels should be monitored every 6 hours and supplemented with an appropriately dosed sliding-scale insulin coverage given subcutaneously as needed to maintain glucose in goal range. Once glucose concentrations are stable, the frequency of measuring capillary glucose concentrations often can be decreased. The insulin dosage in the PN formulation is modified daily based on the amount of insulin given with sliding-scale insulin coverage over the previous 24 hours. If hyperglycemia persists when 0.3 units of insulin per gram of PN dextrose is exceeded, initiation of a separate intravenous insulin infusion should be used to achieve more appropriate glycemic control. In a patient whose insulin needs are dynamic or difficult to predict (e.g. infection, inflammatory response), a separate intravenous infusion is preferred.

Another method of medication administration with PN is co-infusion through the same intravenous tubing. This should be avoided unless physical and chemical compatibility of the medication with the PN formulation is assured prior to its administration in this manner. Studies of medication compatibility with PN found that the compatibility differed for TNA versus 2-in-1 formulations, emphasizing that compatibility in one formulation does not predict compatibility in the other. As such, compatibility information should be derived for PN that closely match the formulation prescribed for the patient in question. If the medication is not compatible with PN, the PN infusion should not be interrupted for medication administration. The medication should be administered via another intravenous route. Finally, the compatibility of some medications with a TNA may be dependent on drug concentration. For example, morphine sulfate is compatible with TNA at a concentration of 1 mg/ml but not 15 mg/ml.

PRACTICE GUIDELINES
1. The dose, admixture preparation, packaging, delivery process, and storage and administration method should be confirmed to ensure that the PN is stable and all components are compatible.
2. The responsible pharmacist should verify that the administration of drugs with PN either admixed in the PN or co-infused through the same intravenous tubing is safe, clinically appropriate, stable, and free from incompatibilities.
3. If there is no information concerning compatibility of the medication with PN, it should be administered separately from the PN.
4. Compatibility information should be evaluated according to concentration of the medication used.
and whether the base formulation is a 2-in-1 or a TNA.
5. Insulin use in PN should be done in a consistent manner according to a method that healthcare personnel have adequate knowledge.
6. Decisions related to stability and compatibility are made according to the most reliable information available from the literature or manufacturer of intravenous nutrients. If no information exists, stability and compatibility of the PN shall be determined in consultation with the manufacturer before it is dispensed to the patient.
7. Given the limited amount of published stability information available, the use of a 2-in-1 formulation with separate administration of IVFE is recommended for neonatal/infant patients.

REFERENCES

SECTION VII: PARENTERAL NUTRITION ADMINISTRATION

Optimal, safe PN administration requires an adequate understanding of multiple integrated key concepts. Comments from respondents to the 2003 Survey of PN Practices noted several problems with administration including: incorrect PN rate and volume and PN administered to the wrong patient or via the wrong venous access site. This section will address the concepts pertinent to safe administration of PN including: proper venous access device selection, care and assessment; appropriate use of the medical equipment needed to deliver the PN solution; the chemical properties of the PN formulation itself and monitoring the patient’s response to the PN therapy. The institutional use of PN from home or another facility is an issue addressed in this section.

VENOUS ACCESS SELECTION, CARE AND ASSESSMENT

To safely and properly administer PN, the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters and appropriate infection control measures to prevent catheter-related infections shall be understood.

The proper selection of a venous access site (central vs peripheral vein) depends on nutrient requirements and duration of PN.\(^1\) Due to the hypertonic nature of most PN formulations, it is recommended that the PN be administered through a central venous access catheter (CVC) with tip placement in the superior vena cava\(^2\) adjacent to the right atrium.\(^4\) Proper catheter tip placement also reduces the risk for cardiac injury\(^7\) and decreases the chance for problems infusing or withdrawing fluids from the catheter.\(^4\) Infusion of PN via a peripheral vein requires careful consideration of the formulation’s osmolality along with judicious monitoring of the venous access site for signs of phlebitis and/or infiltration. Since 10% and 20% IVFE products are isotonic, they may be infused separately via a peripheral vein or as part of a TNA when osmolality does not exceed 900 mOsm/L.\(^8\)

In general, selection of the most appropriate parenteral access device is based on the patient’s vascular condition, vascular anatomy, vascular access history, type and duration of therapy, coagulation status, care setting (acute care, long-term care, and home care) and underlying disease. Additional considerations when selecting a venous access device for PN include the patient’s physical ability to care for the catheter, cognitive function, activity level, body image concerns and caregiver involvement. Temporary percutaneous non-tunneled CVCs (subclavian, jugular) are most often used in the acute care setting for short duration therapy. Femoral CVC’s are associated with a higher risk of venous thrombosis and catheter related sepsis; they are not recommended for PN administration unless no other venous access can be attained.\(^9\) In circumstances where the tip of the femoral catheter is not located in the inferior vena cava, adjustment of the PN content to effectively reduce the osmolality similar to peripheral PN is recommended. Care and maintenance of the femoral catheter should be with the same vigilance as any other CVC. Tunneled percutaneous catheters (e.g. Hickman®, Groshong®) or implanted subcutaneous infusion ports are most appropriate for long-term therapy outside of the acute care setting. The peripherally inserted central catheter (PICC) for central venous access is used for PN administration in a variety of health care settings. The PICC is a reasonable CVC option to consider if the anticipated length of PN is weeks and not long-term provided the appropriate placement of the catheter tip can be achieved and verified. Generally, tunneled catheters or implanted ports should be considered for longer access durations and more permanent therapy.
Guidelines have been developed for the daily care and maintenance of the catheter once the proper CVC is inserted.\textsuperscript{3,6} Prior to the initial administration of PN through a CVC, and any other time there are signs/symptoms indicative of a compromised catheter position, the catheter tip location shall be verified radiographically. Proper catheter tip placement shall also be confirmed and or validated in the pediatric patient as growth and maturity occur. The infectious complications of PN administration are also reduced when catheter access devices are dedicated solely to PN usage (or the designation of one port solely for PN administration if a multi-lumen catheter is used) and catheter manipulations are minimized.\textsuperscript{3} Reductions in catheter associated sepsis have been reported when nurses are educated in the proper care of the CVC based on established standards and guidelines.\textsuperscript{1,8} If continued care and monitoring is required beyond the acute care setting, it is the health care provider’s responsibility to ensure education of the patient and/or caregiver in proper care techniques.

MEDICAL EQUIPMENT FOR PN ADMINISTRATION

Filters

The use of in-line filters has been recommended during the administration of intravenous products such as PN formulations.\textsuperscript{6,10–12} The rationale for this recommendation is related to the filter’s ability to eliminate or reduce infusion of particulates, microprecipitates, microorganisms, pyrogens and air. Due to the multiple additives used to prepare PN formulations, a large number of particulates may contaminate the fluid being administered. Particles of 5 microns or larger are capable of obstructing blood flow, which could lead to complications such as pulmonary embolism. These foreign particles may also produce phlebitis at the injection site, a therapy-limiting problem when PN is administered peripherally. An in-line filter can reduce the incidence of phlebitis.

Microprecipitates form under certain pH and temperature conditions such that the rate and extent are dependent on these factors in addition to the concentration of PN additives. Microprecipitates of calcium phosphate are known to cause serious problems. Initial visual inspection of PN is a primary method to avoid problems with microprecipitates but this cannot be relied upon since it is unlikely the precipitate will form instantaneously. In most situations, precipitates may take hours to develop. As such, visual inspection of the PN formulation should be done periodically throughout the compounding, dispensing and administration processes. Visual detection is limited however since particles <50 microns cannot be easily detected with the unaided eye and problems are possible with particles of this size. Since particles may clog filters, filters have been criticized because they may require frequent nursing interventions. It should be recognized that a clogged filter and associated infusion pump alarm is a potential sign of a precipitate. It is never appropriate to remove a clogged filter and allow the formulation to infuse without a filter.

Use of a 0.22 micron filter for PN administration can remove microorganisms but this practice is limited to use with 2-in-1 formulations. The integrity of the IVFE is compromised when infused through filters <1.2 microns in size. A 1.2 micron filter however does not remove most microorganisms from a contaminated PN formulation even though it is effective in removing particulates and microprecipitates. PN formulations are considered high-risk admixtures and can become contaminated during compounding or administration setup. There have been frequent reports of patient infections caused by contaminated PN fluids. The use of aseptic technique in preparation and administration of PN formulations is critical to avoid infections due to contaminated PN formulations.

Filters have been shown to be effective in removing pyrogens from 2-in-1 formulations and those with air venting can prevent air emboli. The use of filters may reduce the potential for contaminated PN formulations to infect a patient but do not eliminate the possibility. As such, the CDC does not recommend in-line filters solely for infection control purposes.\textsuperscript{3}

Use of in-line filters has limitations. They can cause decreased flow rates, clogs, or air locks. This may lead to increased manipulation of the intravenous administration set, creating a potential for microbial contamination. For PN administration, a 0.22 micron filter is recommended for a 2-in-1 formulation. A 1.2 micron filter should be used for TNA. When considering particulate and microprecipitate contamination only, a 1.2 micron filter can be used for all PN formulations.

Infusion Pumps and Administration Sets

Specific recommendations also exist to guide the use of PN administration tubing sets. PN administration sets shall be changed using aseptic technique and universal precautions.\textsuperscript{3} Changes of “add on devices” to the PN administration set (e.g., extension tubing, filters or needle-less devices) should coincide with changing of the PN administration set to maintain the entire PN administration system as a closed system.\textsuperscript{3} TNA administration sets are changed every 24 hours and immediately upon suspected contamination or if the product integrity has been compromised.\textsuperscript{2,3,6} Administration sets used for separate IVFE infusions (not TNA) are discarded after each unit is infused, unless additional units are administered consecutively. When separate IVFE infusions are administered consecutively, the administration set shall be replaced every 24 hours.\textsuperscript{3,6} As with TNA, lipid emulsion sets are changed immediately if contamination is suspected or if the product integrity has been compromised. Administration sets infusing PN formulations containing only dextrose and amino acids shall be changed every 72 hours.\textsuperscript{3} PN final containers and administration sets free of the plasticizer; di (2-ethylhexyl) phthalate (DEHP) shall be used to prevent DEHP contamination of TNAs or separate IVFE infusions.\textsuperscript{13} Since DEHP is highly lipophilic, IVFE are capable of extracting DEHP from the polyvinylchloride (PVC) final containers and administration sets. Concern over adverse effects from DEHP is related to its potential for neurotoxicity, car-
cinogenicity, and hepatotoxicity in animals. Use of DEHP-free bags and tubing is especially important in chronic long-term patients, pregnant patients, and pediatric patients receiving PN.

Intravenous (IV) infusion pumps are an integral component of PN administration. Use of an electronic infusion pump to safely administer PN is recommended. Infusion pumps assure accurate volume (rate) control and contain safety alarms (visual and auditory) for sensing air and pressure changes in the IV tubing; some pumps also have a programmable rate cycling feature to minimize infusion errors. These features are important to PN because of the hypertonic nature, fluid volume, dextrose and potassium content of PN formulations. JCAHO National Patient Safety Goals include recommendations for infusion pumps. Free-flow protection is important to the safety of PN administration to avoid serious harm caused by rapid administration of potassium and dextrose. Regular preventative maintenance and testing should assure proper functioning of clinical alarm systems because health care practitioners administering the PN, and individuals receiving the PN, rely on those alerts to optimize safe infusion of the PN formulation.

Safe administration guidelines are not only intended to protect those patients receiving PN, they are also important to protect the health care provider administering PN from blood-borne pathogens. Health care providers face daily exposure to blood when administering PN via a venous access device. Among the risks are human immunodeficiency virus (HIV), hepatitis B and hepatitis C. Federal government agencies have published standards to prevent needle-stick injuries in health care settings, as well as, enforcement procedures for the occupational exposure to blood-borne pathogens. In 2000, the Needle-stick Safety and Prevention Act was signed into law and in 2001, incorporated into the revised OSHA Blood-borne Pathogen Directive. The Act highlights the importance of using new technologies and requires employers who are currently covered by the Blood-borne Pathogen Standard to evaluate and implement medical devices that reduce the risk of needle-stick injuries, as well as, eliminate or reduce exposure to blood-borne pathogens. Health care providers administering PN should take an active role in identifying, evaluating and selecting effective medical devices to reduce their exposure to blood-borne pathogens. Examples of compliance for PN administration is the use of a commercially available needle-less system to draw blood or applying a needle-free catheter patency device to a CVC to eliminate the back flow of blood into the catheter lumen. It is important to note that the Needle-stick Safety and Prevention Act changes OSHA’s 1991 Blood-borne Pathogens Standard from an “agency directive” to a law, enforceable in the same manner as any other OSHA public law.

**ADMINISTRATION ISSUES RELATED TO PN ADMIXTURE PROPERTIES**

Prior to PN administration, the identity of the patient is verified using at least two identifiers. The PN label is reviewed for accuracy, expiration date and patient identity. Also, the PN formulation and container is visually inspected for leaks, color changes, emulsion cracking, clarity and expiration dates. Do not use any parenteral fluid that has expired, has visual turbidity, leaks, emulsion cracking or particulate matter. The TNA presents a more complex scenario for inspection because of the inability to visualize precipitate or particulate matter in the opaque admixture. It is essential to visually assess the TNA for destabilization or separation of the lipid components. Any TNA that exhibits evidence of destabilization (heavy creaming, cracking or discoloration) shall not be administered or shall be discontinued immediately if the solution is already infusing. The pharmacist evaluates the TNA formulation before dispensing, and the nurse, patient and/or caregiver is responsible for ongoing evaluation of the TNA while it is infusing.

As discussed previously, IV medications are frequently prescribed for patients receiving PN. Published information regarding PN compatibility with parenteral medications is available, but limited. The appropriate administration of parenteral medications to individuals receiving PN is based on stability and compatibility data. It is recommended that stability and compatibility data be validated if the medication is expected to have direct contact with the PN. If an incompatibility or unstable condition exists, or if there is no information available, the medication should be administered separate from the PN.

The characteristics of IVFE favor an environment in which pathogenic organisms can thrive. These 10% and 20% preparations are nearly iso-osmotic (250–290 mOsm/L), have a near-neutral alkaline pH (pH = 7.5), and contain glycerol, all of which are conducive to the growth of microorganisms. However, when IVFE are combined with crystalline amino acids and hydrated dextrose to form TNA, the pH drops (pH ~ 6.0) and the osmolarity increases to provide a poor growth medium. Several reports of microbial growth potential in commercially available IVFE bottles prompted the Centers for Disease Control and Prevention in 1982 to limit the “hang time” to 12 hours after the manufacturer’s container is spiked with the appropriate administration set. IVFE have been associated with reports of fungemia in the neonatal population, including both Candida species and Malassezia furfur. It appears that IVFE were administered as separate infusions in these reports. When IVFE is transferred from its original container to another sterile device (e.g., syringe) or recipient container for infusion separate from PN, one could argue that a more conservative 6-hour hang time should be followed. This recommendation would be consistent with the FDA-approved labeling for propofol (Diprivan®) emulsion when manipulated for administration via a syringe delivery system, even with the existence of antimicrobial agents not present in IVFE manufactured for nutritional use. A standard for product dating of prepared sterile dosage forms when the product is altered from its original packaging has recently been revised by the United States Pharmacopeia (USP). The USP refers to this newly assigned date as the “beyond-use date” and it limits the time period in which the product can be used in patients.
Because of the concern for microbial contamination, the USP recommends that IVFE products be used within 12 hours of opening the original container if they are to be infused as a separate infusion. The infusion rate should not exceed 0.125 g/kg/hr, thus a 200-mL bottle of 20% IVFE should not be infused more rapidly than over 6 hours (0.095 g/kg/hour) in the 70-kg reference man. If a slower infusion is desirable and the selected rate of administration exceeds 12 hours, then the lipids shall be given in two separate bottles so as not to exceed a 12 hour hang time for any single container. If the IVFE is admixed directly to the PN to form a TNA, the final PN formulation can be infused over a 24-hour period since it provides a safe vehicle with respect to infectious risks.

**Patient Response to PN Administration**

No discussion of safe PN administration would be complete without briefly mentioning a few key monitoring concepts unique to the patients receiving PN. Considerable cost and serious complications are often associated with PN administration. Once it is determined that the individual will receive PN, goals for nutrition support should be set with specific markers and outcomes to be measured. These goals may include improved or replenished protein stores, normalization of clinical laboratory values, and reduction in morbidity/mortality and improvement in quality of life or optimization of clinical outcomes. Monitoring individuals receiving PN is necessary to determine the efficacy of the specialized nutrition therapy; detect and prevent complications; evaluate changes in clinical condition and document clinical outcomes. All patients receiving PN should be monitored for fluid and electrolyte imbalances, proper blood glucose control and signs/symptoms of CVC infections. Typically, laboratory monitoring of serum chemistries and visceral proteins are more frequent when PN is initiated and then decrease in frequency as clinically indicated. The health care provider is also alert to potential changes in fluid status and should closely monitor intake and output, edema, vital signs and weights with attention to changes, patterns or trends that could indicate problems or progress toward achieving nutritional goals. Regular assessment and meticulous care of the parenteral access device assures a reliable delivery system for the PN and minimizes the chance for infection. It is important that the healthcare provider periodically compare the actual PN nutrients delivered to the patient with the recommended measured or estimated nutrition needs to assure optimal treatment. Patients may tolerate the PN infusion better if the refrigerated PN is removed from the refrigerator 30–60 minutes prior to the scheduled infusion times; PN patients occasionally complain of discomfort while the chilled solution is infused into the central circulation. Individuals receiving their first PN formulation should be monitored closely for any adverse reactions. Compatibility and stability of a new parenteral medication shall be assured along with a review of the medication profile for potential effects on safe administration of other medications. It is also important to reassess gastrointestinal function and readiness for oral/enteral feeding if the patient’s clinical condition should change.

**IVFE infusion in hypertriglyceremic patients.** Confusion surrounds the safe administration of IVFE in patients with hypertriglyceridemia. As previously mentioned, several investigators have determined that the rate for infusion of IVFE not exceed 0.125 g/kg/hour in order to avoid serious metabolic effects. Thus, IVFE should be infused at rates to avoid serum triglyceride levels >400 mg/dL in adults and >200 mg/dL in neonates. The clinical consequences associated with hypertriglyceridemia in both adults and neonates include an increased risk of pancreatitis, immunosuppression, and altered pulmonary hemodynamics, while hypertriglyceridemia in the preterm infant with physiologic jaundice and hyperbilirubinemia (>18 mg/dL) is associated with kernicterus. Doses of IVFE should be limited to the provision of EFAs (e.g., 250 mL of 20% IVFE, once or twice weekly) when triglyceride concentrations rise above 400 mg/dL in adult patients. Temporary interruption of IVFE infusions for 12 to 24 hours are recommended when serum triglyceride concentrations exceed 275 mg/dL in neonates and infants; a decrease in infusion rate by 0.02–0.04 g/kg/hour is suggested when IVFE infusions are restarted. Withholding IVFE in adults shall be considered when serum triglyceride concentrations are greater than 500 mg/dL. The presence of excess phospholipid content of 10% versus 20% IVFE is also associated with greater plasma lipid alterations. The excess phospholipids produce lipoprotein X-like substances that can compete with chylomicron remnants for hepatocyte binding sites. This can interfere with lipid clearance by delaying peripheral hydrolysis of triglycerides by lipoprotein lipase. Use of 20% IVFE allows for more efficient triglyceride clearance and metabolism.

**Use of PN Prepared by Another Facility**

Organizations commonly admit patients from another facility or home who are receiving PN. The admission may or may not be directly related to the PN or underlying disease. These organizations are frequently in the position of dealing with PN formulations brought in from home or infusing into patients transferred from other inpatient facilities. Due to the complex nature of PN formulations from a dosing, compatibility, sterility and stability perspective, the use of the PN by the organization is a difficult issue. Evidence to support, guide or describe current practices is lacking so the issue was addressed in the 2003 Survey of PN Practices. As discussed in the introduction, there was no consensus as to whether PN formulations compounded elsewhere should be administered in the admitting organization’s facility. Several points for consideration (pro or con) were identified in the comments to the survey question along with Task Force input (Table I).
If the PN was infusing at the time of patient admission, responders to the question stated that it was allowed to finish then the hospital pharmacy prepared all subsequent PN formulations. In another scenario, if the PN was compounded by the health care systems’ own home infusion pharmacy, the PN was allowed to be used.

There is no consensus to the problems addressed therefore; it is difficult to provide specific guidelines. Guidelines for use of oral medications from home referred to as ‘bring-in’ medications (i.e., patient’s own supply) have been developed and may provide some insight when considering PN formulations brought in from an outside facility. Principles addressed in these guidelines are outlined as follows:

- The use of a patient’s own supply in the hospital should be avoided unless they are not obtainable by the pharmacy;
- If used, a physician order shall be written.
  - The identity of the medication should be verified
  - If not identifiable, it shall not be used.
- It should be dispensed as a part of the pharmacy distribution system, not separate from it.

PN formulations are much more complex than oral medications. It may also be prudent to consider the following for PN:

- A policy and procedure is developed to address the issue.
- When the use of PN is allowed, a physician’s order is required.
  - All components of the PN formulation are entered into the patient’s medical record as an active order.
- Issues related to maintaining PN integrity during storage, delivery and administration are resolved.
- If there is any reason that the compounding or storage conditions of the PN formulation have been compromised, its use shall not be allowed.
- The appropriateness of the PN formulation for the patient’s current condition is assured prior to its administration.

### PRACTICE GUIDELINES

1. Central PN is administered via a CVC with the distal tip placed in the superior vena cava adjacent to the right atrium.
2. The use of femoral catheters for PN administration should be avoided.
3. Proper CVC tip placement shall be confirmed prior to initial PN administration and/or any other time signs/symptoms indicate an improper catheter position. Proper CVC tip placement shall also be confirmed/validated in the pediatric patient when there has been significant growth.
4. Care and maintain venous catheters used for PN according to published standards.
5. Equipment used to administer PN formulations shall be selected based on the safest mode of delivery for both the patient and the healthcare provider.
6. A 1.2 micron filter may be used for all PN formulations. Alternatively a 0.22 micron filter may be used for 2-in-1 formulations.
7. A filter that clogs during PN infusion may be indicative of a problem and may be replaced but shall never be removed.
8. PN final containers and administration sets shall be free of the plasticizer, DEHP if IVFE is a component of the nutrient regimen.
9. Administration sets for IVFE infusions separate from PN formulations shall be discarded after use or if the IVFE is infused continuously, at least every 24 hours.
10. Administration sets for TNA are changed every 24 hours.
11. Administration sets for 2-in-1 formulations are changed every 72 hours.
12. PN is to be administered via an infusion pump having adequate protection from ‘free flow’ and reliable, audible alarms.
13. Medical devices for PN administration should be used that minimize risk of needle-stick injuries and exposure to blood-borne pathogens.
14. Prior to PN administration, the patient’s identity is verified and the PN label is reviewed for accuracy and expiration dates.
15. Visually inspect each PN prior to administration, do not infuse the PN formulation if visual changes or precipitates are apparent.
16. The PN infusion shall be completed within 24 hours of initiating the infusion.
17. IVFE infused separately from PN formulations shall be completed within 12 hours of entry into the original container.
18. The patient receiving PN should be monitored to determine the efficacy of the PN therapy; detect and prevent complications; evaluate changes in clinical conditions; and document clinical outcomes.
19. A policy and procedure should be in place to deal with the use of PN formulations prepared by an outside facility.

### TABLE I

<table>
<thead>
<tr>
<th>Reasons for use</th>
<th>Reasons not to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevents wastage of unused home PN</td>
<td>Inability to adequately validate PN integrity from a stability and sterility perspective</td>
</tr>
<tr>
<td>Provides specific information concerning PN contents and therapy</td>
<td>Creates billing and reimbursement issues</td>
</tr>
<tr>
<td>PN formula may contain products not available to admitting organization</td>
<td>Medico-legal responsibility for PN administration problems unclear</td>
</tr>
<tr>
<td>Avoids an interruption in therapy</td>
<td>Unfamiliar PN tubing set or infusion pump</td>
</tr>
</tbody>
</table>

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REFERENCES


**Errata**


*Table II*. Determining the Estimated Osmolarity of PN Formulations (found on page S45) should be corrected as follows:

<table>
<thead>
<tr>
<th>PN component</th>
<th>mOsm</th>
<th>Example, 1 L volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PN content</td>
<td>mOsm/L</td>
</tr>
<tr>
<td>Dextrose</td>
<td>170 g</td>
<td>850</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>60 g</td>
<td>600</td>
</tr>
<tr>
<td>Fat Emulsion, 20%</td>
<td>20 g</td>
<td>26–30</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>243 mEq</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total = 1719–1723</strong></td>
</tr>
</tbody>
</table>

Based on approximations of the osmolarity of the PN components and used as an estimate only.