PROVISION OF PN NUTRIENTS: WHERE TO MIX IT BEST

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Provision of PN Nutrients: Where to Mix It Best

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Learning Objectives

1. Know different methods of PN preparation
2. Know the European legal regulation and basic requirements in PN compounding
3. Know quality assurance and control aspects in the PN compounding
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### Table 1
Different methods of PN admixtures preparation.

<table>
<thead>
<tr>
<th>Mixing method</th>
<th>Product of mixing</th>
<th>Additives which should be added in order to obtain complete PN admixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic preparation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- amino acids solution(^a)</td>
<td>By filling separate bag</td>
<td>Bag 125–4000 ml</td>
</tr>
<tr>
<td>- glucose solution(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- water and/or electrolyte solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- fat emulsion in separate bottles or containers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two chamber bag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- containing amino acids and glucose solutions in two separate chambers without or with fixed amount of electrolytes</td>
<td>By breaking of peelable seals</td>
<td>Bag 1000–2000 ml</td>
</tr>
<tr>
<td>Three chamber bag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- containing amino acids solution, glucose solution and fat emulsion in 3 separate chambers with fixed amount of electrolytes</td>
<td>By breaking of peelable seals.</td>
<td>Bag 1000–2500 ml</td>
</tr>
<tr>
<td>Industrial mix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- containing mixture of amino acids, glucose, fat emulsion and fixed amount of electrolytes in one ready to use bag, stored under refrigeration</td>
<td>Already mixed</td>
<td>Already mixed</td>
</tr>
</tbody>
</table>

\(^a\) With or without electrolytes.  
\(^b\) Stability data are necessary and therefore preparation in hospital pharmacy is recommended.
# PN Delivery Systems

## Multibottle Systems  ➡️  All-in-One (AiO) Systems

<table>
<thead>
<tr>
<th></th>
<th>Bottles with single components</th>
<th>Bottles with combined components</th>
<th>Two in one Admixtures</th>
<th>All-in-one (3 in 1) admixtures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>Glucose</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>Lipid</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>Ready-to-use</td>
<td>(-)</td>
<td>(+)</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

*Fig. 1. Two-in-One (TIO) and All-in-One (AiO) systems for parenteral nutrition.*

*Mühlbach et al, in: Basics in Clinical Nutrition, 2011*
Multibottle Systems

- Not easy/inconvenient to use
- High risk of contamination
- Wastage of solutions
- High cost
Ready-to-Use Multi-Chamber Bags

- Commercially-manufactured
- Ready-to-use formulations in multi-chamber bags (MCBs)

**Container polymer**
(multi-layered container foil allows sterilization)

**Cover wrap**
(oxygen protection)

- **Injection port**
- **Sealing**
- **Infusion port**

**Lipid** — **Amino acids** — **Glucose**
Before use:

- To mix the components, break the seal between the chambers mechanically within the outer bag container in a closed system (asepsis).
Ready-to-Use Multi-Chamber Bags

Formulation osmolarity is <600-900 mOsm/L

Adapted from PN guidelines DGEM, Ger Med Sci, 2009
PN Compounding

Compounding

Manual

Automated (Compounder)
Manual PN Compounding

• Separate addition of nutrients via:
  • syringe and needle delivery
  • with the aid of sterile solution transfer sets.

• The order of mixing is important
• Pharmaceutical calculations needed
## Determining the Estimated Osmolarity of PN Formulations

<table>
<thead>
<tr>
<th>PN component</th>
<th>mOsm</th>
<th>Example, 1 L volume</th>
<th></th>
<th>mOsm/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PN content</td>
<td>mOsm</td>
<td></td>
</tr>
<tr>
<td>Dextrose</td>
<td>5 per gram</td>
<td>170 g</td>
<td>850</td>
<td></td>
</tr>
<tr>
<td>Amino Acids</td>
<td>10 per gram</td>
<td>60 g</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Fat Emulsion, 20%</td>
<td>1.3–1.5 per gram (product dependent)</td>
<td>20 g</td>
<td>26–30</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>1 per mEq</td>
<td>243 mEq</td>
<td>243</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total = 1719–1723</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- Software program
- Check the appropriateness of final product
- Compounding of each component according to manufacturer’s recommendation.
## Ready to Use Multi-Chamber Bags vs Compounding

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shelf life</strong></td>
<td>Longer in ready to use multi-chamber bags</td>
</tr>
<tr>
<td><strong>Macronutrients</strong></td>
<td>Minor differences</td>
</tr>
<tr>
<td><strong>Long term (home) treatment</strong></td>
<td>Individualized admixtures needed</td>
</tr>
<tr>
<td><strong>Pediatrics- neonates</strong></td>
<td>Individualized admixtures needed</td>
</tr>
<tr>
<td><strong>Cost-Effectiveness</strong></td>
<td>More studies needed</td>
</tr>
</tbody>
</table>
Recommendations on Storage of PN

• PN bags should be used within 24 h after preparation if stored at room temperature, or within 7 days if stored at 4°C.
  – the risk of microbiological contamination and physicochemical changes are expected to increase with storage time.

• Industrially-manufactured multi-chamber bags can be stored for periods of months to years as specified by the manufacturer.
  – the stability of added components such as vitamins is limited and often does not exceed 24 h at room temperature.

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1. Know different methods of PN preparation

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European Regulations and Legislations

• The first European directive of medicinal product was introduced in the 1965, but the compounding activity of the pharmacies was not considered.

• Concept of compounding was introduced with the Directive 89/341/CE that amended Directives 65/65/CE.

• Updated in the Directive 2001/83/CE
Original Article

Economic assessment of aseptic compounding rooms in hospital pharmacies in five European countries

Bérengère Dekyndt¹, Bertrand Décaudin¹,², Damien Lannoy¹,² and Pascal Odou¹,²

Indeed, the issue of recommendations or mandatory regulations to hospitals and pharmacies has allowed pharmacists to rely on several texts to ensure the quality of their pharmaceutical preparations. These documents include:

- ISO standard: particularly with ISO 14644¹;
- Current Good Manufacturing Practices² (cGMP);
- United State Pharmacopeia Chapter 797³ (USP 797);
- European Pharmacopeia⁴-⁶: Specific monographs of parenteral and sterile preparations;
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme⁷ (PIC/S); and
- CM/resAP 2011⁸ resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.

Moreover, French pharmacists refer to chapters 6 and 7 of the Bonnes pratiques de préparation⁹ (BPP; French Good Compounding Practices for Hospitals and Community Pharmacies).
• Method of preparation of sterile products
USP General Chapter <797>
Pharmaceutical Compounding
– Sterile Preparations
Reprinted from USP 42—NF 37

Links for Supplemental Resources
• Information on USP General Chapter <797>
• USP General Chapter <797> FAQs
• USP General Chapter <797> Education Courses
• Sign up for USP Updates

This text is a courtesy copy of General Chapter <797> Pharmaceutical Compounding – Sterile Preparations, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – sterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.
EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)
PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS
Resolution CM/Res(2016)1
on quality and safety assurance requirements for medicinal products
prepared in pharmacies for the special needs of patients

(Succeeding Resolution CM/ResAP(2011)1
on quality and safety assurance requirements for medicinal products
prepared in pharmacies for the special needs of patients)

(Adopted by the Committee of Ministers on 1 June 2016
at the 1258th meeting of the Ministers’ Deputies)

This Resolution aims to harmonize quality and safety assurance and standards for
pharmacy-prepared medicinal products among the European countries and to fill the
gap in quality and safety assurance between preparation in pharmacies and
medicinal produced by the pharmaceutical industry.
Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container
Bonnes pratiques de préparation
Organisation, regulations, preparation and logistics of parenteral nutrition in hospitals and homes; the role of the nutrition support team – Guidelines on Parenteral Nutrition, Chapter 8

Abstract
PN (parenteral nutrition) should be standardised to ensure quality and to reduce complications, and it should be carried out in consultation with a specialised nutrition support team whenever possible. Interdisciplinary nutrition support teams should be established in all hospitals because effectiveness and efficiency in the implementation of PN are increased. The tasks of the team include improvements of quality of care as well as enhancing the benefit to cost ratio. Therapeutic decisions must be taken by attending physicians, who should collaborate with the nutrition support team. “All-in-One” bags are generally preferred for PN in hospitals and may be industrially manufactured, industrially manufactured with the necessity to add micronutrients, or be prepared ‘on-demand’ within or outside the hospital according to a standardised or individual composition and under consideration of sterile and aseptic conditions. A standardised procedure should be established for introduction and advancement of enteral or oral nutrition. Home PN may be indicated if the expected duration of when PN exceeds 4 weeks. Home PN is a well-established method for providing long-term PN, which should be indicated by the attending physician and be reviewed by the nutrition support team. The care of home PN patients should be standardised whenever possible. The indication for home PN should be regularly reviewed during the course of PN.

Keywords: nutrition support team, organisation of PN, compounding, multi-chamber bags, home parenteral nutrition

Zusammenfassung
Die parenterale Ernährung (PE) im Krankenhaus sollte standardisiert werden um die Qualität zu erhöhen und die Komplikationsraten zu reduzieren. PN sollte soweit möglich in Konsultation mit einem spezialisierten Ernährungsteam durchgeführt werden. Ein interdisziplinär arbeitendes Ernährungsteam sollte in allen Krankenhäusern eingerichtet werden, um die Effektivität und die Effizienz der Durchführung der Ernährungstherapie zu verbessern. Die Aufgaben des Teams sind vielseitig und beinhalten u.a. die Verbesserung der ernährungsmedizinischen Qualität sowie die Wirtschaftlichkeit. Die Indikation zu medizinischen Maßnahmen einschließlich der PE muss durch den behandelnden Arzt gestellt werden und sollte unter Einbezug des Ernährungsteams erfolgen. „All-in-One“-Beutel werden generell für die PE im Krankenhaus bevorzugt und können entweder vollständig industriell hergestellt, industriell hergestellt mit der Notwendigkeit individueller Zugaben von Mikronährstoffen, oder innerhalb bzw. außerhalb des Krankenhauses nach
A STANDARD PROTOCOL for DERIVATION and ASSESSMENT of STABILITY

Part 4 – Parenteral Nutrition

1st Edition

May 2016
## Clean Room and Clean Air Device Classification

### Table 2. ISO Classification of Particulate Matter in Room Air (Limits Given in Particles of $\geq 0.5$ mcm/m$^3$)

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Particle Limit per m$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>35.2</td>
</tr>
<tr>
<td>4</td>
<td>352</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td><strong>3,520</strong></td>
</tr>
<tr>
<td>6</td>
<td>35,200</td>
</tr>
<tr>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
</tr>
</tbody>
</table>

**Note:** (Class A – Class 100)

Clean Room
Aseptic Compounding: Cleaning

Wiping with a residue-free disinfecting agent such as sterile 70% isopropyl alcohol is recommended, which is allowed to dry before compounding begins.

**USP 797**

### Table 3. Minimum Frequency of Cleaning and Disinfecting Compounding Areas

<table>
<thead>
<tr>
<th>Site</th>
<th>Minimum Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5 (see Table 1) Primary Engineering Control (e.g., LAFW,</td>
<td></td>
</tr>
<tr>
<td>BSC, CAI, CACI)</td>
<td>At the beginning of each shift, before each batch, not longer than 30 minutes</td>
</tr>
<tr>
<td></td>
<td>following the previous surface disinfection when ongoing compounding activities</td>
</tr>
<tr>
<td></td>
<td>are occurring, after spills, and when surface contamination is known or</td>
</tr>
<tr>
<td></td>
<td>suspected</td>
</tr>
<tr>
<td>Counters and easily cleanable work surfaces</td>
<td>Daily</td>
</tr>
<tr>
<td>Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Walls</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
</tr>
<tr>
<td>Storage shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
Aseptic Compounding: Personnel Training

• Establishing **minimum competency standards for all personnel** who have access to and operate the compounder.

• Personnel are required to **wear clean gowns or cover-alls**.

• Gloves, masks, hair covers, shoe covers and removal of hand, finger and wrist jewelry are recommended during the compounding process.

Recommendations

- In hospitals PN bags should be prepared at the hospital pharmacy under sterile conditions according to agreed quality assurance guidelines (B).

- Additions of micronutrients or other components to PN bags must be performed under aseptic conditions, and they should preferably be added under a Laminar Airflow according to good manufacturing practice (GMP) standards (C).

Learning Objectives

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Final Product: Quality Control

- Weight/volume
- pH
- Electrolyte levels
  - Glucose and amino acid concentrations
  - Osmolarity
- Refractive Index
Checking for Stability Problems

- Calcium phosphate precipitation
  - Amounts are critical especially for neonates

**Risk Factors for Ca-Phosphate Precipitation**

- pH
- calcium and phosphate concentrations
- kind of calcium and phosphate salts
- magnesium concentration
- amino acid solution composition and concentration
- glucose concentration
- presence of lipid emulsion
- mixing order
- time period since admixing
- temperature
- infusion rate
- co-infusion with drugs and drugs added

Checking for Stability Problems

- Calcium phosphate precipitation
  - Amounts are critical especially for neonates
- Lipid peroxidation

The higher the content of polyunsaturated fatty acid (PUFA), the higher the probability of peroxidation:

- Soybean / Fish Oil (> 60% PUFA)
- LCT/MCT (~40% PUFA)
- Olive Oil (~20% PUFA)

Other factors that increase peroxidation risk:
- Trace elements,
- Temperature
- Exposure to direct sunlight
Checking for Stability Problems

- Calcium phosphate precipitation
  - Amounts are critical especially for neonates
- Lipid peroxidation
- Lipid emulsion stability

Lipid Emulsion Stability

In the presence of high concentrations of di- and tri-valent cations (electrolytes, trace elements) bridges with the negatively charged emulsifiers (lecithin) are formed and decrease the negative surface potential of the lipid droplets (retracting forces).

Check Final Product

- Each PN formulation compounded **should be visually inspected** for signs of gross particulate contamination, particulate formation and/or phase separation.
  - The process generally includes a detailed assessment of the final formulation against a dark background under high-intensity illumination.

**The absence of any obvious physical signs of incompatibility, visual clarity does not equate with safety.**
Microbial Stability

Microbial sterility testing

- When and how to take samples
  - Final product vs starting components
  - When in the process
  - Number and volume

- Sampling of syringes
Microbial Stability

• The microbiological contamination of syringes reconstituted by intensive care nurses varied from 7% to 44%.

• In a pharmacy with qualified personnel and a controlled environment, these percentages are regularly much lower (1%) (p<0.001).

Filtration of medicinal products which cannot be sterilised in their final container

110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.
Correct PN Labeling

- Patient’s name
- Day of administration
- Rate / duration of administration [ml/hr]
- Composition (dose vs. conc.)
- Expiry date (hanging time)
- Storage condition

A pharmaceutical preparation is considered safe also if it is correctly labelled.

Adapted from Pharm. aspects PN support, ESPEN Basics in Clin. Nutrition, 2011.
Recommendations: Where to mix it best?

• PN admixtures should where possible be manufactured under the best possible aseptic conditions:
  ✓ in the pharmacy based clean room
  ✓ with the trained personnel for strict aseptic techniques

• If the hospital does not have a suitable pharmacy manufacturing unit, consider:
  ✓ purchasing ready-made PN admixtures from commercial compounding centers
  ✓ using industrially produced ready-made formulations

• Only if these conditions do not exist (i.e. in an emergency or during out of hours time periods or lack of suitable conditions in hospital pharmacy) ward based preparation should be considered.
Take Home Messages

• Develop policies and procedures for your own institute
• Routine education of pharmacy staff is necessary
• Strict aseptic technique and clean room environment is important
• Consensus on up-to-date and clear international/worldwide guidelines is needed.
• Storage conditions, content of PN admixtures, temperature, mixing order should be appropriate.
Thank you for your attention...
Ca-Phosphate Precipitation

The stability of inorganic phosphate and calcium ceases when molar concentration of calcium times concentration of phosphate is over 72 (Ca++mmol/lxPmmol/l<72).


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

We cannot make a recommendation due to the multiple variations in amino acid concentrations, PN volume, pH, presence or absence of fat emulsion, or the amounts of other minerals (eg, magnesium). We suggest published graphs for specific products provide adequate guidance; however, no evidence indicates that these formulations remain stable for >24–48 h. 

Ca-Phosphate Precipitation

- Inline filter may not prevent infusion of precipitates.
  - The precipitate may be formed on the patient side of the inline filter as the admixture is warmed by the patient’s body.

- A well defined admixing sequence is mandatory to avoid precipitation due to incorrect dilution of nutrients during compounding
  - 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.

Ca-Phosphate Precipitation

• The use of organic phosphate may be an alternative way of avoiding solubility problems with Ca and phosphate.

• Ca gluconate is the preferred form of Ca used in multi-component PN formulations.
  – Ca chloride is far more reactive than an equivalent amount of Ca gluconate salt.

• Bicarbonate reacts with Ca to form the insoluble product Ca carbonate. If an alkalinizing salt is indicated, then sodium or potassium acetate should be used, not bicarbonate salts.

Vitamin Stability

- Vitamin C (ascorbic acid): Oxidation
- Vitamin A (retinol): Photolysis and binding to plastic
- Vitamin B2 (riboflavin): Photolysis
- Vitamin E: Photooxidation
The Maillard Reaction (the browning reaction)

- The complexation of carbohydrates by certain amino acids (such as lysine, tryptophane, serine, threonine, methionine, arginine, glycine, isoleucine) 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.
Adding Medications into the PN Solutions

**Insulin**
When regular insulin added into the PN solution 35% of insulin may adsorb to the bag within 24 hours.

**Albumin**
It is not recommended to add because of physical and chemical incompatibility, stability impairment, infection risk.

**H₂ antagonists**
It has been shown that continuous infusion of H2 antagonists is more effective in regulating stomach pH.

**Heparin**
Addition of heparin to the PN solution results in creaming-like stability problems in the final solution.
