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THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

ESPEN LLL Course
Topic 9 - Approach to Parenteral Nutrition

Education and Culture DG
Lifelong Learning Programme

Pharmaceutical aspects of PN: Compounding and ready-to-use preparation

Module 9.3

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Acknowledgement to

Stefan Mühlebach

Learning objectives

To know the different systems for PN delivery (advantages and limits)

To know the challenges and risks of compounding / ready-to-use preparation of AiO PN admixtures (responsibilities: GMP, incompatibilities, ME)

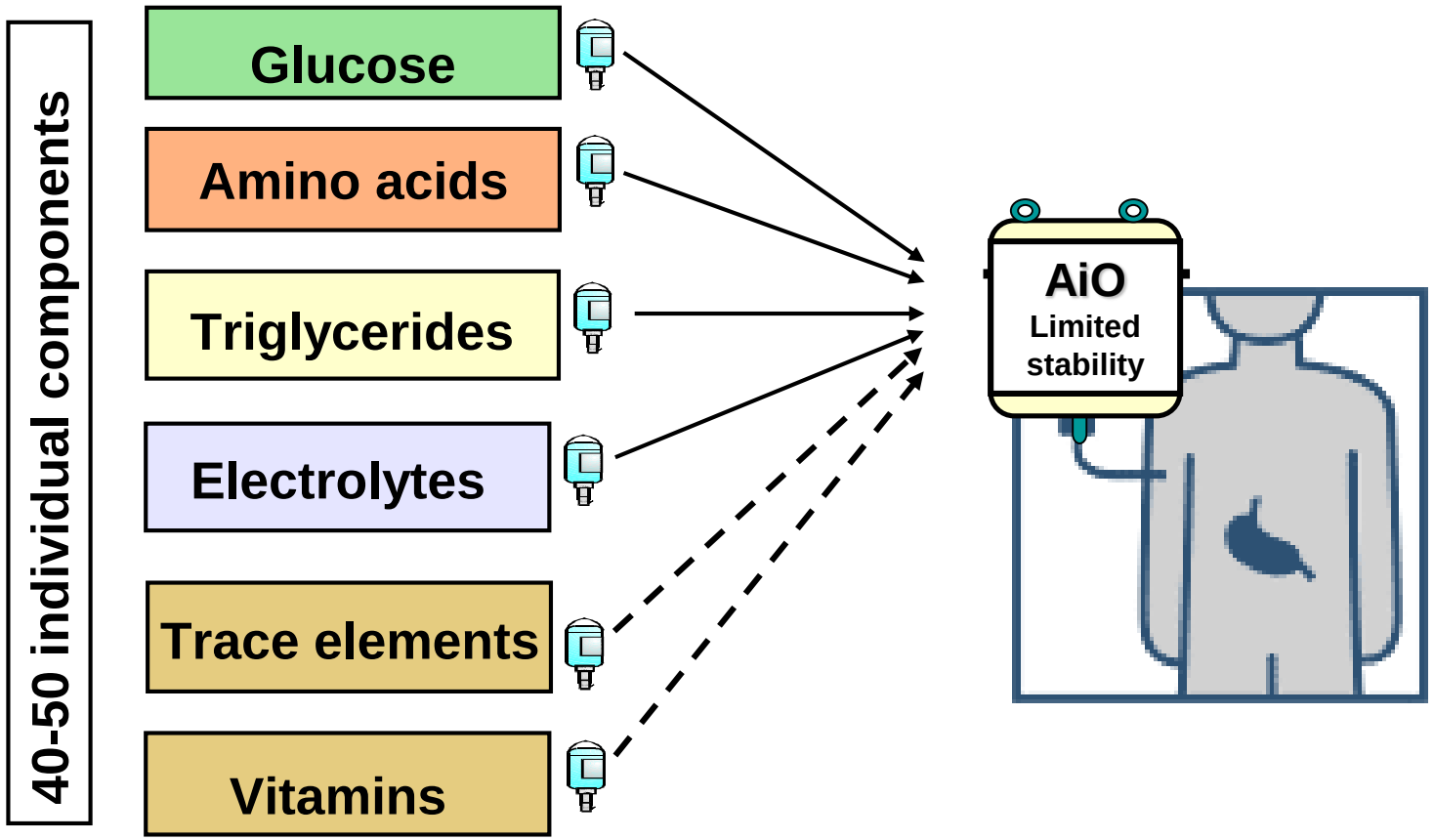
To understand the general advice not to admix drugs to PN AiO admixtures in absence of specific data (physicochemical and microbial instabilities)

To apply a risk-benefit approach for drug adding to a PN AiO admixture (interactions; compatibility documentation) (quality, efficacy, safety, convenience)

Layout

- Introduction
  - PN delivery systems;
    the AiO admixture concept and its realisation
  - PN a multi-professional task, its challenges and risks (Nutrition Support Team role)
  - Stable industrial PN admixtures (premixes)
  - Correct labelling
- PN compounding and ready to use admixing
  - GMP (aseptic preparation)
  - Compatibility and stability
  - Drug admixing
- Summary

The AiO admixture concept (adults)

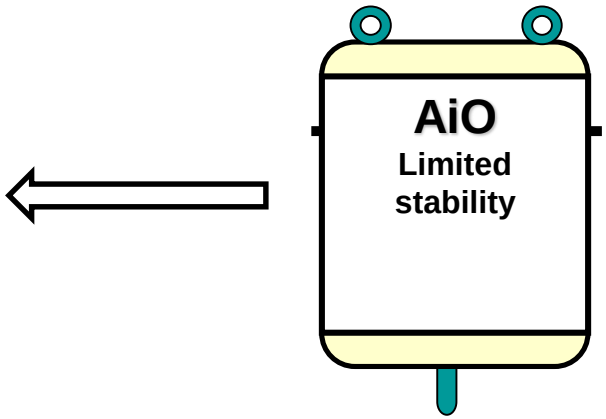


Adapted from Mühlebach
Curr Opin Clin Nutr Metabol Care, 2005

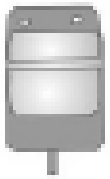
The AiO admixture concept (adults)

- Amino acid (AA) - **4 kcal/g**
- Glucose - **3.4 kcal/g** (4 kcal/g)
- Lipid (triglycerides) - **9 kcal/g**

- **Energy: 20-25 (-35) kcal/kg/d**
- **AA: 0.8-1.5 g/kg/d** (100-150 kcal/g N)
- **Lipid: 0.5-1 (-2) g/kg/d** (EFA 7-10g/d)
- **Glucose: 3-6 g/kg/d** (blood gluc <10mM)
- **Water: 30-40 ml/kg/d**
- **Electrolytes**
- **Vitamins and trace elements**



PN delivery systems

	Containers with single components	Containers with combined components	Two-in-one admixtures	All-in-one admixtures
Amino acids				
Glucose (dextrose)				
Lipids				
Ready-to-use	**(-)**	**(+)**	**+**	**+ +**

Mühlebach et al, in: Basics in Clinical Nutrition 4th ed, 2011

Clinical nutrition a multi-professional process

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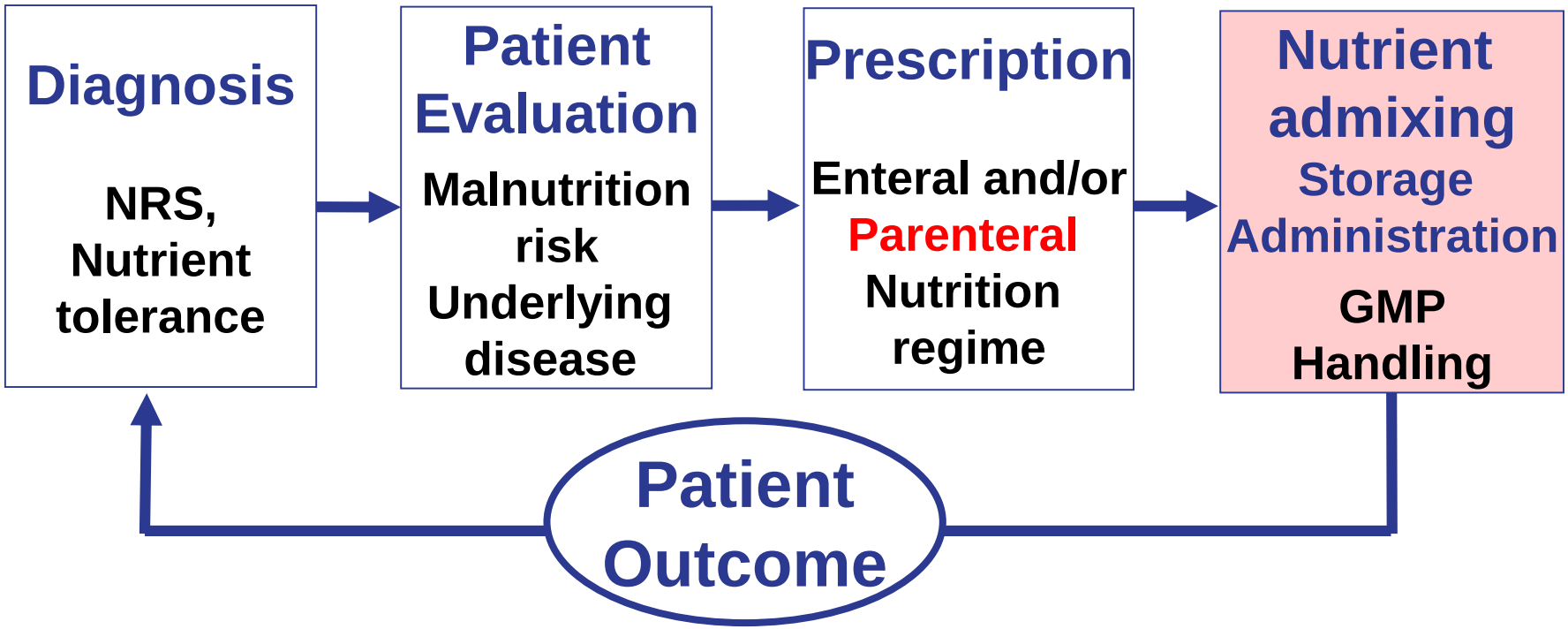
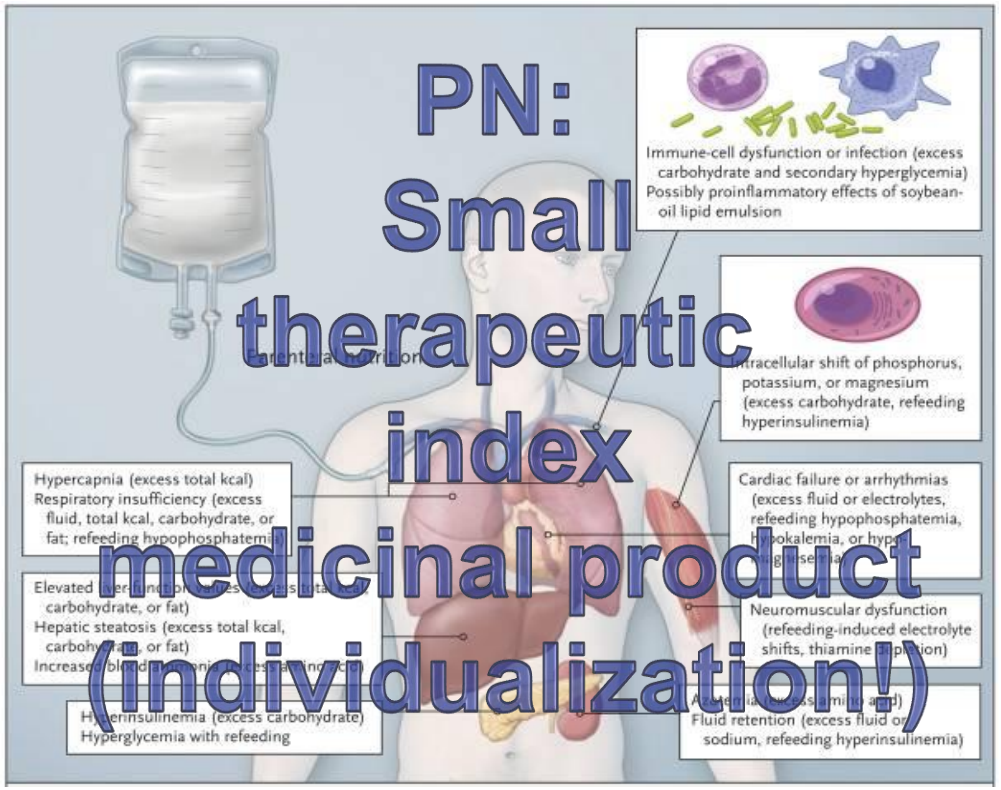
Nutrition Support Team (NST)



Adapted from Mühlebach,
Aktuel Ernaehr Med 2002

PN-related complications (often avoidable ME)



Nutrient effect (qual., quant, dose over time):

-**Metabolic** (electrolyte and water imbalances), **clinical and immunologic effect**

-**Physico-chemical reactions** (stability, safety, drug interactions)

-**Infection risk**

Ziegler, NEJM, 2009

Challenges in PN (history)

Type	Issue
✓ Parenteral formulation of nutrients	Pharmaceutical
✓ Hypertonic solutions for volume reduction	Pharmaceutical
✓ Long-term (central) venous access and material tolerance (catheters)	Technical
✓ Practicability/convenience, efficacy, safety of (long-term) PN	Medical, Patient care Pharmaceutical
➢ Strict asepsis during compounding, ready to use preparation/administration	Pharmaceutical
➢ Prevention/correction of metabolic, physicochemical adverse effects	Medical Pharmaceutical

Adapted from Dudrick, JPEN, 2003

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Risks associated with PN

- Infective: Microbial contamination, infections
  aseptic compounding/admixing: GMP
- Metabolic: Nutrient administration / intolerance
  PN-associated hyperglycaemia, refeeding syndrome, bone loss...
- Mechanical: Catheter occlusions,
  Compounding/admixing errors: incompatibilities: precipitations…

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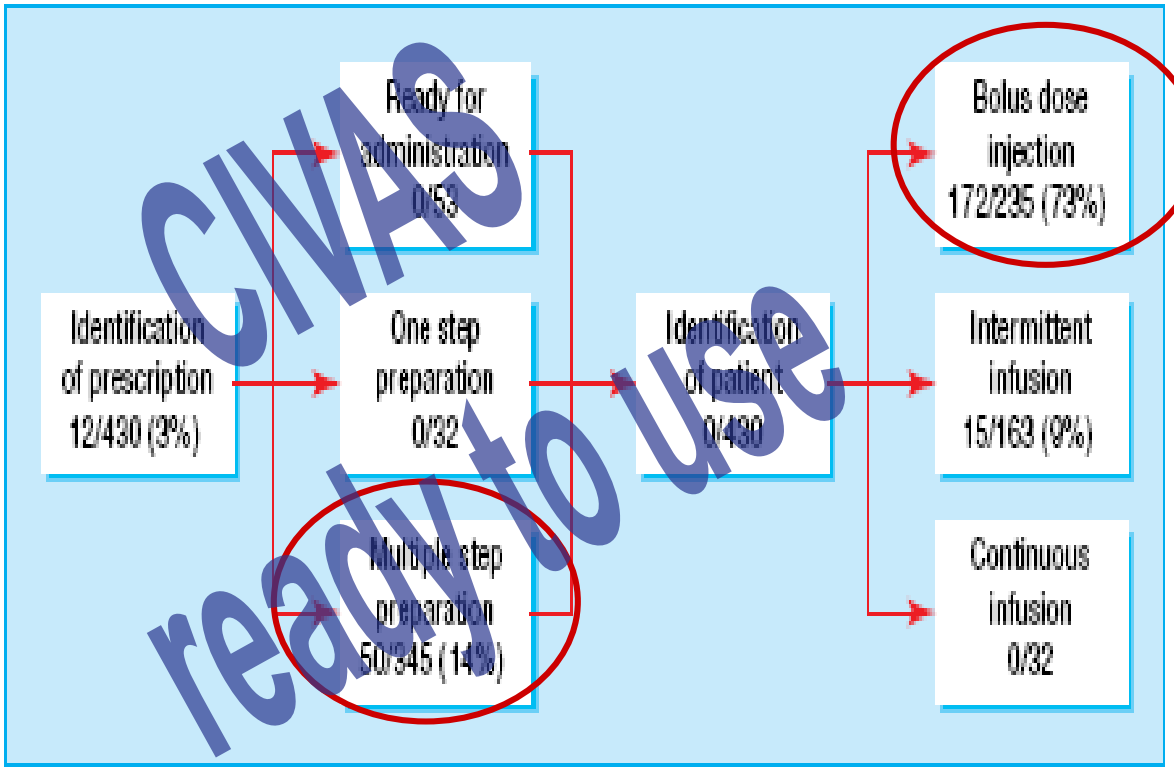
- Toxic: Harmful (reactions) products:
  Fat emulsion deterioration; PUFA: liver dysfunction, oxidative stress; lipid peroxidation
- Incorrectness: (Avoidable!) Medication Errors:
  Ready-to-use preparation: Incorrect components/dosing/timing. Handling, patient care (QoL): Number of IV accesses, stop cocks, (home) PN management, social integration, mobility
- Economical: Indication and use, cost effectiveness
  Regimes: Standard MC bags vs. tailor-made AiO admixtures…

Medication safety: Good practices



What this study adds

Errors occurred in about half of the intravenous drug doses observed

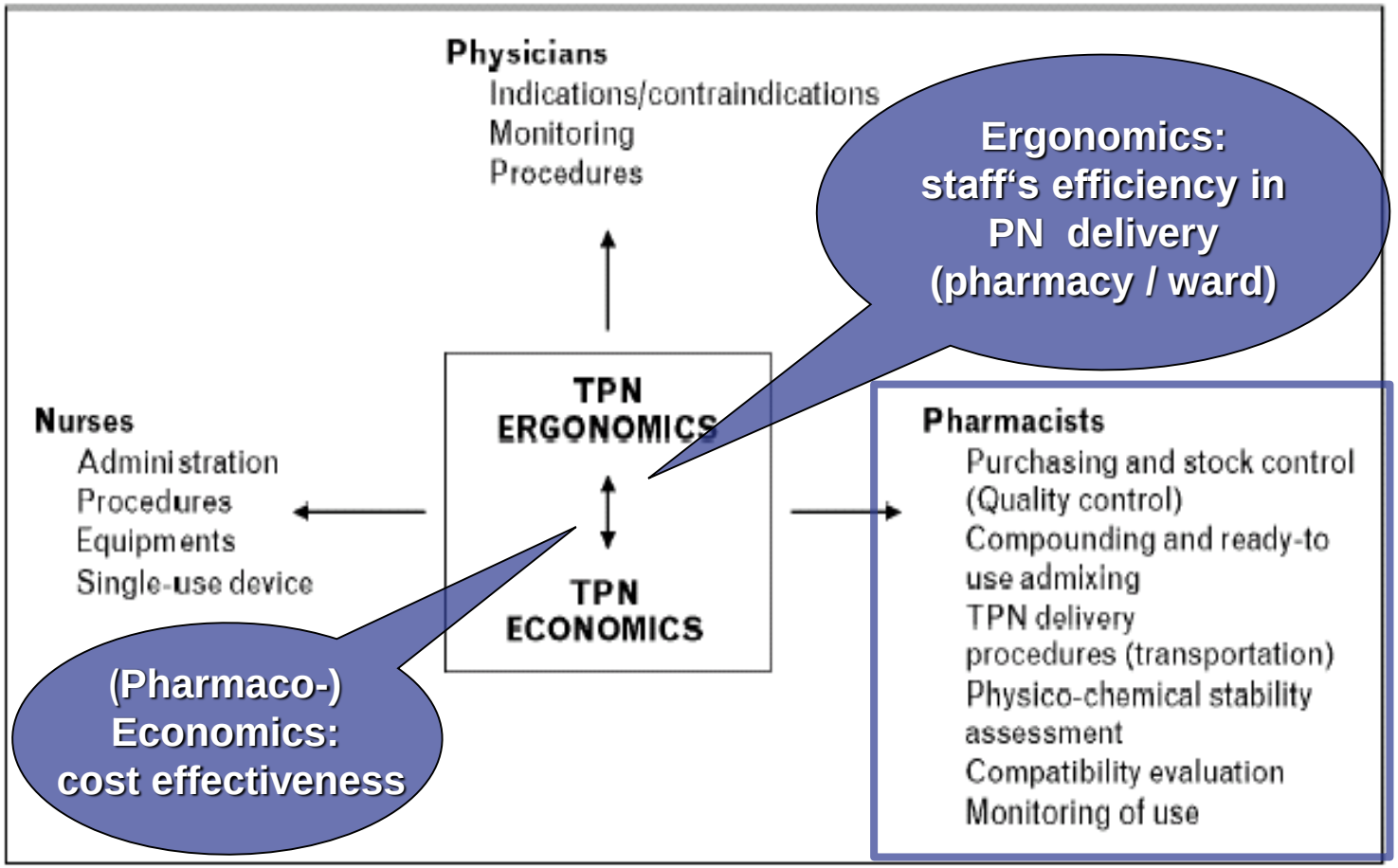
Errors were potentially harmful in about a third of cases

The most common errors were giving bolus doses too quickly and mistakes in preparing drugs that required multiple steps

Stages and errors in preparation and administration of intravenous drugs (numbers of errors/number of observations of each stage)

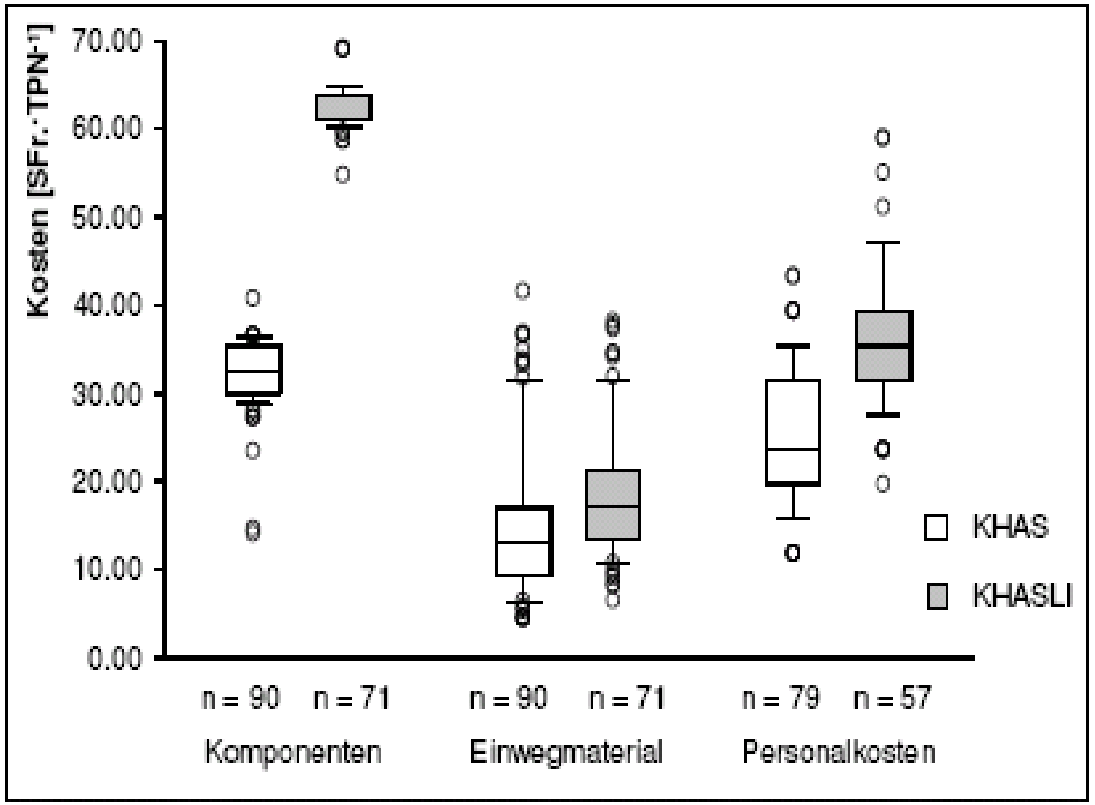
Taxis et al, BMJ, 2003

NST: roles / responsibilities in PN



Genton et al, Curr Opin Clin Nutr Metab Care, 2006

Compounding cost of PN in neonates



Mean cost
(min-max)

CH-AA **CHF 68.95 (100%)**
(CHF 36.75-109.10)

CH-AA-LI **CHF 114.55 (166%)**
(CHF 92.90-140.75)

Gräflein PhD thesis 2004 (http://edoc.unibas.ch/82/1/DissB_6720.pdf)

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In favour of AiO PN admixtures

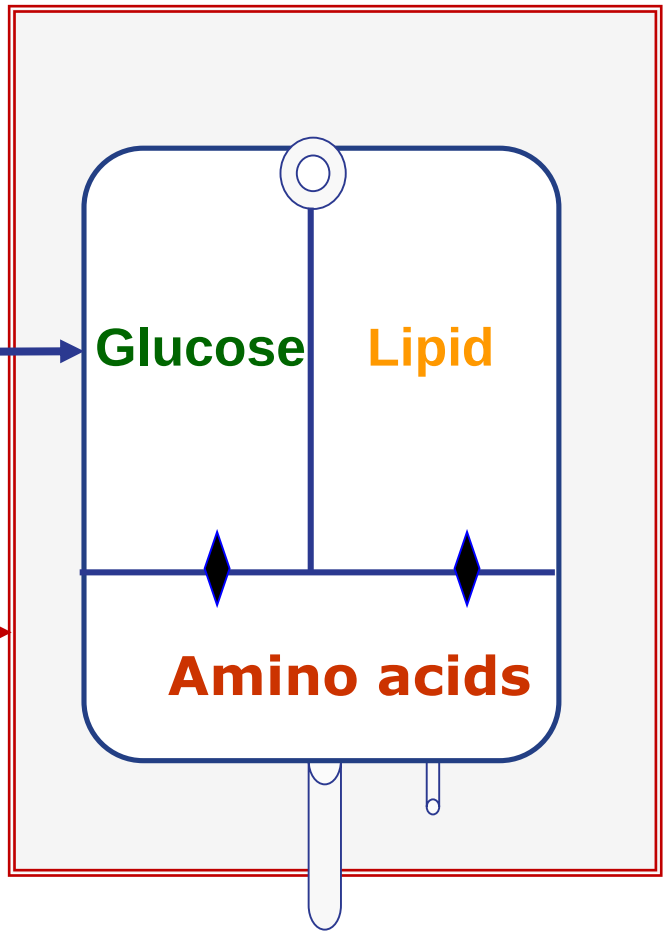
- Safe: daily requirements properly compounded (GMP), documented stability
- Efficient: simultaneous administration of nutrients (metabolic tolerance) in acute and long-term (home) treatment
- Convenient: single container and single line (less handling and risks)

Driscoll, JPEN, 2003

Industrial PN (shelf live): Multi-Chamber (MC) bag

Container polymer
(multi-layered container foil allows sterilization)

Cover wrap
(oxygen protection)



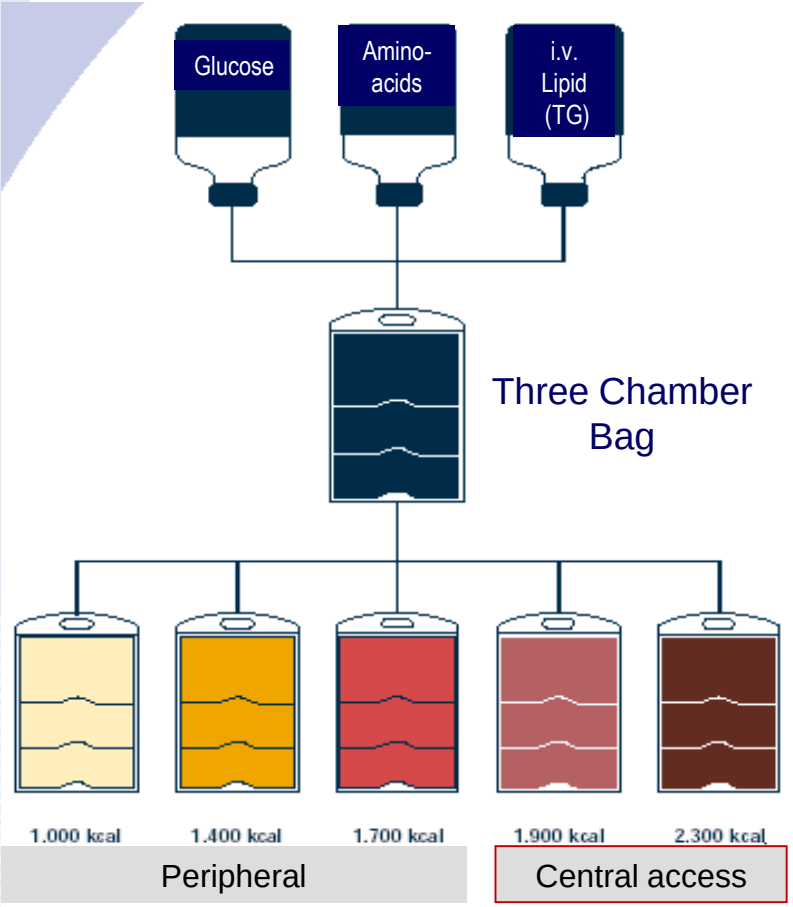
Injection port

sealing

Infusion port

Mühlebach, Curr Opin Clin Nutr Metabol Care, 2005

Commercial 3-C bags (not yet complete!)



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PN osmolarity increase by electrolytes

(central IV access needed if > 800 mosm/kg!)

Electrolyte	Standard PN (mmol/day)	Salt form	Daily dosage mosmol (theoretical)
Na^+	80–100	NaCl	160–200
K^+	60–150	KH_2PO_4	180–450
		KCl	120–300
Ca^{++}	2.5–5	$CaCl_2$	7.5–15
		Ca (organ.)	2.5–5
Mg^{++}	8–12	$MgSO_4$	16–24

Adapted from PN guidelines DGEM, Ger Med Sci, 2009

Correct PN labelling

- Patient's name
- Day of administration
- Rate / duration of administration [ml/hr]
- Composition (dose vs. conc.!)
- Lot identification
- Expiry date (hanging time)
- Storage condition
- Any other specific requirements

- ✓ The right product
- ✓ To the right patient
- ✓ At the right time
- ✓ In the right manner (storage, administration)
- ✓ Traceable

Adapted from Pharmaceutical aspects in PN support, Chap. 6.2.3
ESPEN Basics in Clinical Nutrition 4th edition, 2011

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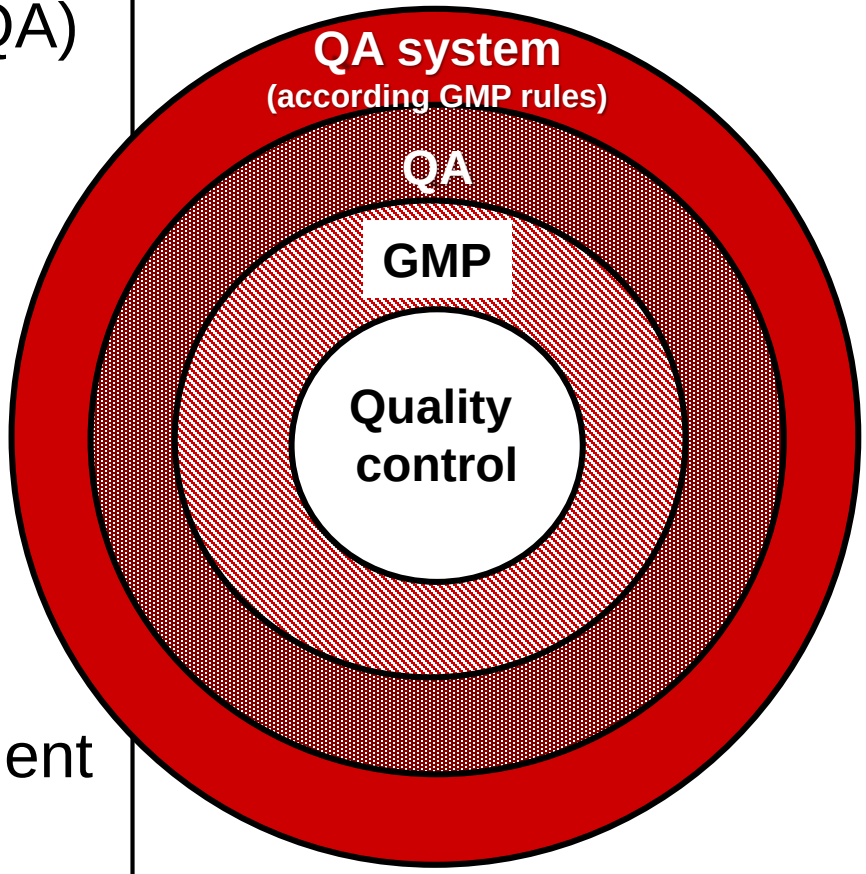
GMP chapters (WHO, Pharmacopoeias)

1. Quality assurance (QA) system
2. Personnel / staff
3. Rooms / equipment
4. Documentation
5. Production process
6. Quality control (QC)
7. Commissioned manufacture
8. Complaint management
9. Self inspection



GMP for production in small quantities, Swiss Pharmacopoeia 11th ed., Suppl.11.2 (2015)

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Aseptic compounding using a filling machine

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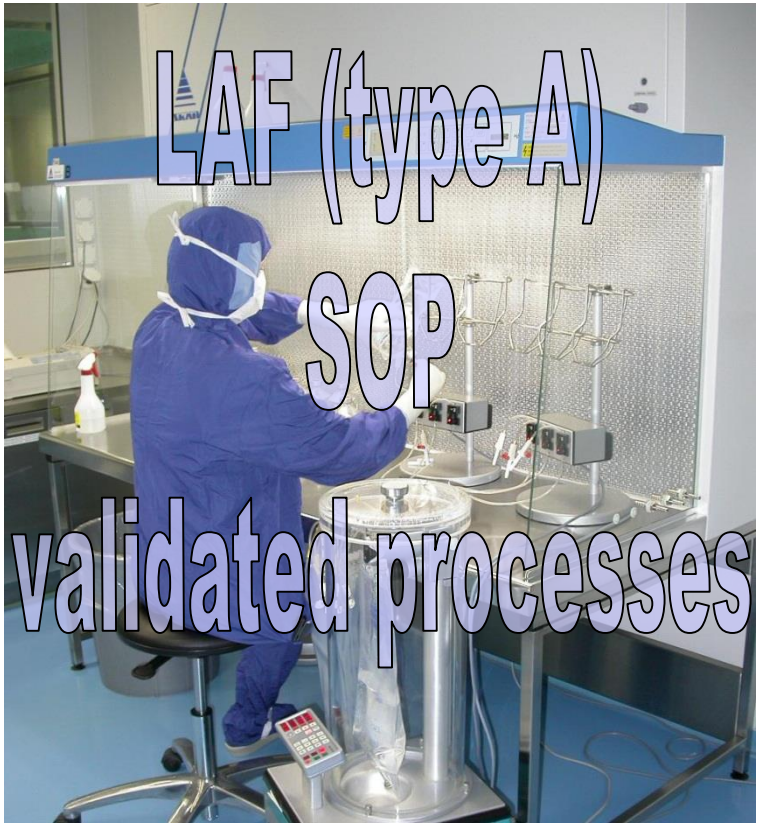
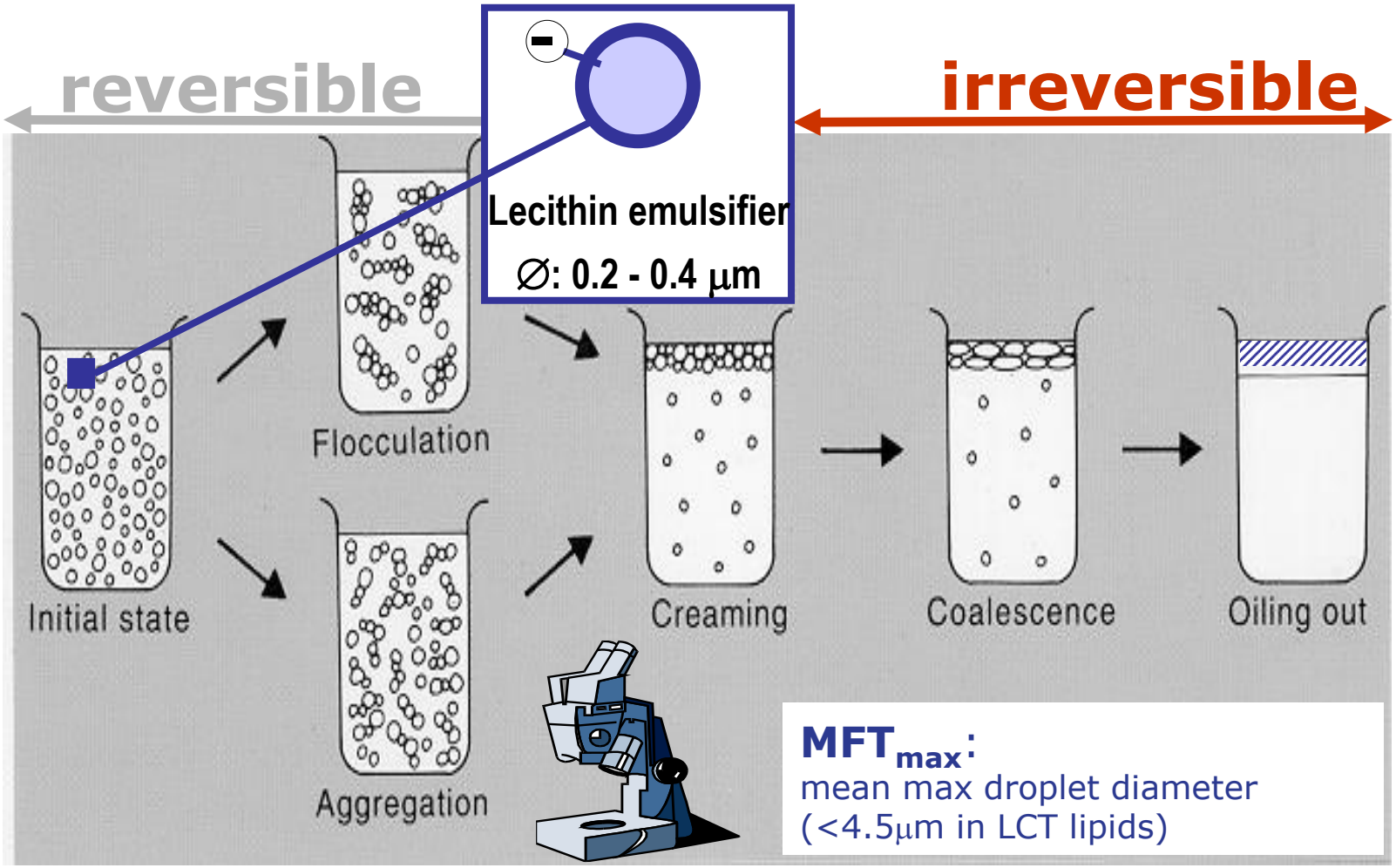


Lipid emulsion destabilisation



Mühlebach et al, in: Basics in Clinical Nutrition, 4th ed. 2011

IV Lipid emulsions for PN (FFA profile)

- LCT (soybean oil):Intralipid®,Lipovenös®
- high Ω-6 PUFA content (linoleic acid)

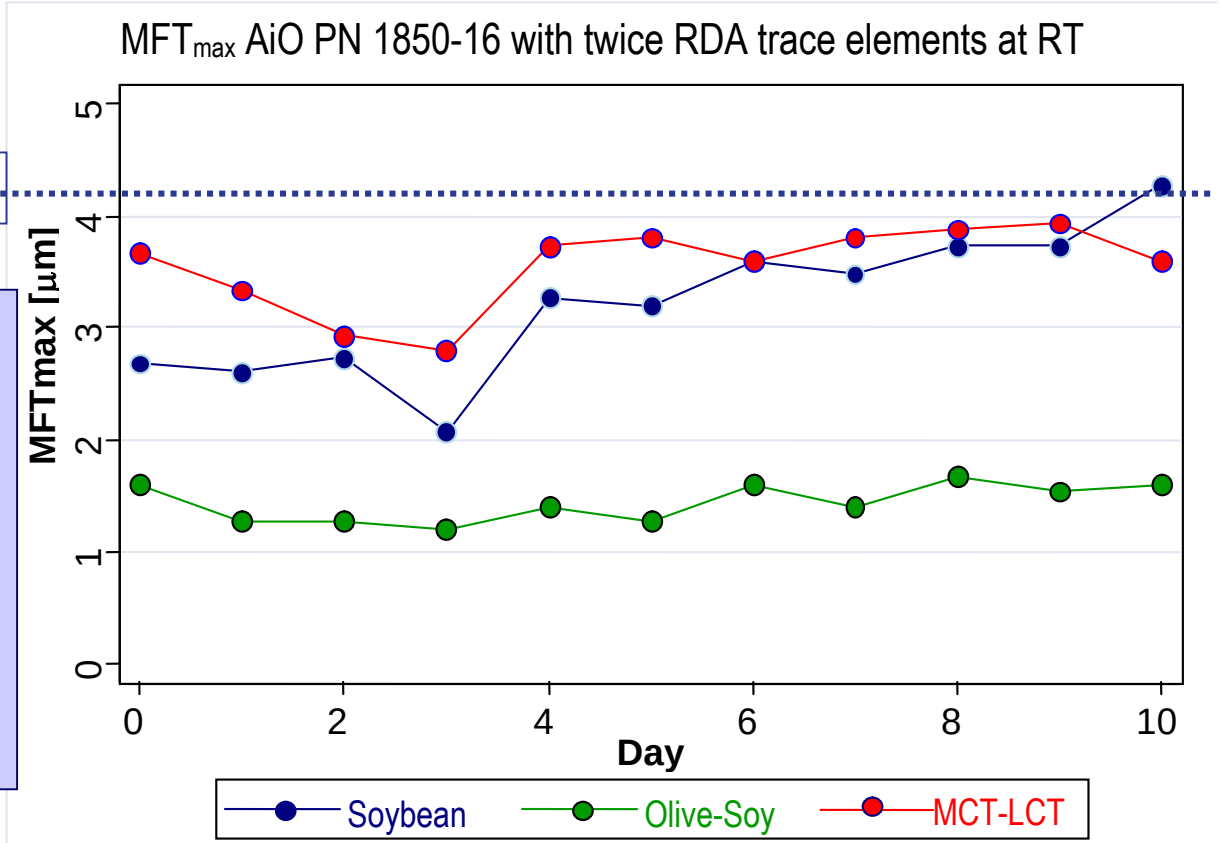
- LCT-MCT mixture: Lipofundin®
- reduced PUFA content

- LCT (olive oil): Clinoleic®
- rich in MUFA (Ω-9 oleic acid) reduced PUFA content

- Structured TG (LC-PUFA, MC): SMOFlipid
- reduced Ω-6/Ω-3 ratio (fish oil)

AIO emulsion stability: Influence of the type of fat

Trace element	RDA i.v. [µMol]	Spur-el KSA
Zn	50-100	50
Fe	20	50
Cu	5-20	5
Se	0.4-0.8	0.3
Mn	3.5	5
Cr	0.2-0.4	0.5
Mo	0.4	0.2
J	1	1
F	0-50	50

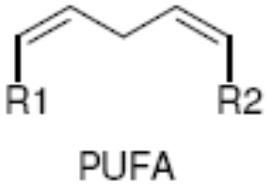


Adapted from Eichenberger et al. e-SPEN, 2006

Lipid peroxidation (LPO)

$^1O_2 + FA \rightarrow OH^\circ + FA^\circ$

Singlet oxygen — Hydroxyl radical



PUFA

$PUFA + OH^\circ \rightarrow PUFA^\circ + H_2O$

Content varies

PUFA radical

Steger et al., Nutrition, 1998

Ca phosphate precipitation

Avoidable Medication Errors

	RDA IV [mmol/kg]	
	Neonates	*Adults*
Calcium	0.5-1.5	0.1-0.2
Phosphate	0.6-1.3	0.1-0.5
Fluid [ml/kg]	120	25 - 30

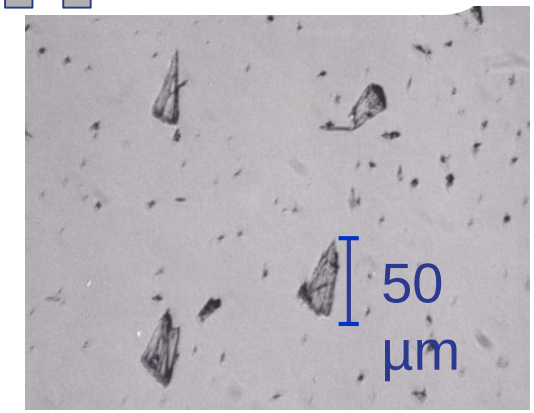
$$Ca^{2+} + H_3PO_4 \longrightarrow Ca(H_2PO_4)_2 + CaHPO_4$$

$$7.2 = pK = pH + \log \frac{[HPO_4]^{2-}}{[H_2PO_4]^{-}}$$

Solubility (H_2O) 20°C*

$Ca(H_2PO_4)_2$ 130 mM

$CaHPO_4$ 2.1 mM



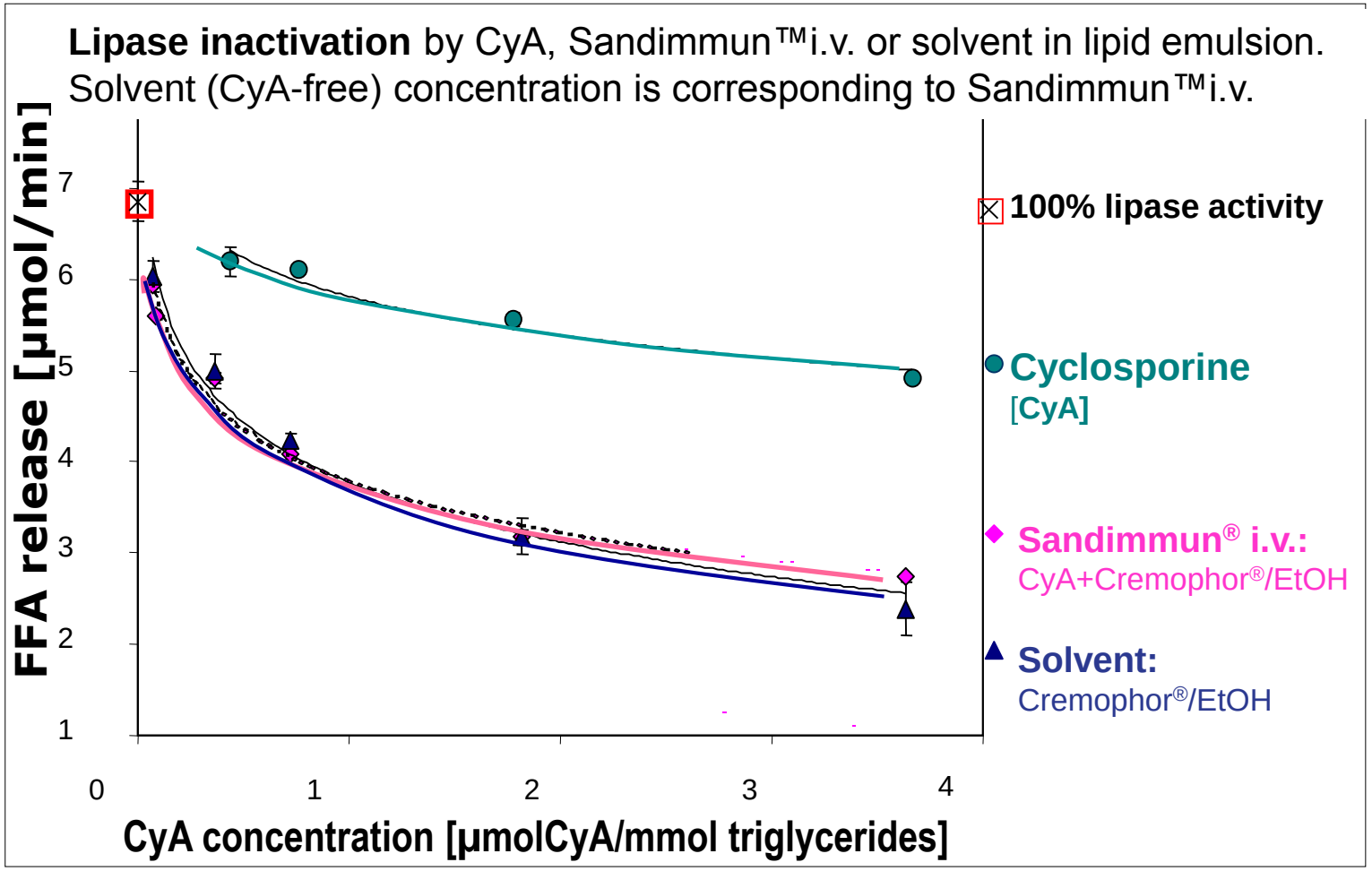
Beware of alkaline solutions (pH > 7.2)

***solubility higher at 2-8°C!**

FDA-Alert: pulmonary emboli: 2 death. Lumpkin, AJHP, 1994

Drug nutrient interaction

Cyclosporine (Sandimmun®) admixed to i.v. Intralipid®



Schmid, thesis ETHZ no.14635; 2002

Guide for PN drug admixing

1. Is there a need for this IV drug?
2. Is there an alternative administration possible outside AiO admixing?
   (different formulation, different administration)
3. Drug profile / characteristics
   (therapeutically, physicochemically)
4. Compatibility documentation / test
   (pharmaceutical expertise)
5. Check for stability and efficacy upon administration

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Summary

- AiO admixtures are the preferred form of PN (safe, efficient, convenient)
- Still need for compounding of tailor-made PN and ready-to-use preparation of commercial MC bags pharmaceutical expertise / responsibility
- GMP and good handling/storage practice are key for safe & efficacious PN
- When drug admixing to PN is necessary, pharmaceutical advice, risk assessment and documentation are mandatory.