Personalise Parenteral Nutrition and Licensed Product First

Are the two mutually exclusive?

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Personalised nutrition – a worthy aim

Evidence and history have demonstrated that both underfeeding and overfeeding can have a detrimental effect on outcomes in health and disease – the mortality due to starvation or the secondary health consequences of obesity, these are obvious in the extremes.

In everyday nutrition support practice, the healthcare professional is faced with uncertainty of what good should look like. We can measure resting energy expenditure but there is still a lack of clarity of how that relates to actual energy expenditure or nutritional metabolic capacity for intake. Protein requirements are even less clear, with no reliable bedside objective measurement of loss and requirement.

The healthcare professional's ability to respond to individual changes in response to nutrients is limited by the modality used. Enteral nutrition (EN) has a wide variety of formulations available. However, they are all essentially fixed ratio formulations; their macronutrient ratios are fixed and are relative to their micronutrient content, giving limited opportunity to personalise calorie, protein, electrolyte and micronutrient delivery independently. Any personalisation is given separately to the main nutrition formula.

Parenteral nutrition (PN) is different. Through compounding, the ability to build a formulation block by block allows for a myriad of different formulation options. This approach provides a different set of challenges for the healthcare professionals responsible for providing these products. It was these challenges, such as sterility assurance, chemical content guarantee, physical and chemical stability, error incidence and production resource, that led the industry to look for alternative solutions.

In the late 1990s, dual chamber (lipid free) and triple chamber (lipid containing) PN products were developed and licensed, with the product range growing over the intervening decades.

How is PN provided?

Over the intervening decades the NHS has moved to a mixed model of PN using both compounded and multichambered bags.

In nutritional circles we talk of 'off-the-shelf', 'standard', 'tailored', 'bespoke' or 'scratch' PN, but these terms mean different things to different organisations. There is no accepted glossary – see **Table 1**.

Each method of PN solution provision has its own risks and challenges, these include quality control, sterility assurance, stability and compatibility, shelf-life and supply chain, resource availability, clinical suitability and timeliness of formulation change and cost. The relative importance or awareness of each of these issues differing at a local level and influencing choice. Each of the presentations above have their own balance of risks.

Quality control

Rigorous quality control is an integral part of the release process of licensed products, the tested content must comply with label requirements before being released by the manufacturer into the market. Quality control of products made in a compounding unit are dependent on the systems and processes used by the individual unit, usually through a process of check and balances, or occasionally with a limited range of end product chemical tests. The complexity of the starting formulation will influence the risks in this process. For example, two additions to a multichambered bag poses a lower risk than a compounded formulation using 13 different starting ingredients.

Sterility assurance

Sterility testing is an integral part of the release process of licensed products, these are sterility guaranteed.

Compounded products can only be sterility assured through safeguards within the aseptic unit designed to reduce the risk of contamination and through proxy measures, such as environmental microbial monitoring. Some providers will undertake sterility testing on products before release, however the current approved tests take two weeks and therefore this is only suitable for batch prepared products with a long shelf-life. For non-MHRA licensed units the shelf-life of compounded products is usually limited to 7 days.

The rate and type of microbial growth supported by PN varies depending on the formulation.[1]

Stability and compatibility

These terms tend to be used interchangeably. Compatibility is the ability to add two or more components together with no detrimental effect on any component. Stability is the duration over which that compatibility is maintained.

Licensed products have been demonstrated to be stable to the end of their shelf-life, both physically and chemically.

Compounded products should have a shelf-life based on published data. However, this data has significant limitations both in the chemical and physical parameters tested and the acceptance limits applied. The majority of PN stability data is based on physical compatibility only, this is due to the primary concern of precipitation and emulsion destabilisation which may cause particles or oil droplets to form and result in vascular occlusion.[2, 3] The range of chemical testing undertaken varies enormously but is usually limited to amino acid content and some vitamin content.

The British Pharmacopeia are developing a monograph for unlicensed PN to introduce some consistency to testing standards for solutions, the final scope of this is still to be defined.

The shelf-life of compounded products is largely dependent on the status of the aseptic facility and the final container type. Unlicensed aseptic units are limited to a maximum shelf-life of 7 days.[4] The most damaging element to PN stability is oxygen. Oxidation causes rapid degradation of vitamin C and lipid emulsion peroxidation and is catalysed by the presence of micronutrients. Multichamber bags are overwrapped in an oxygen barrier plastic film as the primary container does not provide a significant barrier to oxygen. Compounded bags including micronutrients must be compounded into oxygen barrier bags, or multichamber bags with added micronutrients can be re-overwrapped with an oxygen barrier film, to achieve a longer shelf-life.

Resource availability

Determining a patient's nutritional requirements takes the same amount of resource irrespective of the route or method of delivery, it is the prescribing, preparation and administration process that differs depending on the approach used.

Except for a licensed multichamber bag without additions, every PN bag produced will need to be handled by an aseptic unit due to the demands of the NPSA alert. The reduction in NHS investment has resulted in increased demand from commercial compounding units, and at times demand outstrips capacity.

Batch production is usually considered more efficient and has driven some of the standardisation agenda.

Clinical suitability

This is a very subjective issue and is influenced by a number of factors. Licensed multichamber bags contain macronutrients and may contain electrolytes, but they do not contain micronutrients and, therefore, use is limited. In general, these products have been shown to provide acceptable macronutrient ranges and ratios for a significant number of patients, the limiting factor usually being the range stocked by an individual institution.

It may not be possible to give supplemental additives, such as micronutrients or electrolytes, via another route or lumen due the clinical area that the patient is located (nursing skill, nurse to patient ratio or homecare), or issues with vascular access or fluid allowance, or the macronutrient needs may be such that a licensed multichambered bag may not be appropriate. In these instances, aseptic manipulation is required either to a licensed bag or to compound a bag from individual components.

Table 2 contains a summary comparison of the main issues.

If unlicensed compounded solutions are suitable for all patients, why standardise?

The value of standardisation

Standardisation and protocolisation are used throughout healthcare, and other high-risk industries, to control unwarranted variation and mitigate risk.[5] The Carter Review made a series of recommendations in the document 'Operational productivity and performance in English NHS acute hospitals: Unwarranted variations',[6] these included expanding standardisation of PN:

"Opportunities for taking a national or regional approach to collaboration and re-design also exist in the manufacturing and preparation of bespoke medicines in hospitals. Aseptic preparation and supply can be more efficiently and cost effectively delivered through preparing standard doses. We therefore support the introduction of a national agreement to ensure chemotherapy doses are rounded up or down at the point of prescribing to support the delivery of standardised products, which the NHS England Medicines Optimisation Clinical Reference Group is currently developing. A similar standardisation approach should be developed for parental nutrition for both adults and children."

Standardisation has been shown to have benefits in PN prescribing, use and outcomes.

Standardised protocols

The use of protocols for nutrition delivery has been shown to improve nutrient intake in neonates through improved awareness of at-risk patients, early initiation and prescription optimisation,[7] and reduce the risk of prescribing errors in adult patients.[8]

Standardised solutions

Over the last 30 years the use of standardised solutions has been shown to reduce prescription errors,[9] reduce processing and compounding,[9, 10] and reduce the cost of PN provision.[10, 11, 12] A study increasing the use of standardised solutions from 48% to 86% reduced costs by nearly 20% without impacting quality criteria such as nutrient delivery.[13] The same research group have very recently demonstrated that alongside significantly short preparation times and costs, the use of multichamber bags resulted in a reduction in compounding errors when compared to fully compounded bags.[14]

Table 1: PN Terms

Type of bag	What it might be described as
Licensed, commercially available multichamber bag	Off-the-shelf, standard
Licensed, commercially available multichamber bag with additions made in a compounding unit to a fixed formula	Off-the-shelf, standard
Unlicensed compounded formulation made from individual components to a fixed formula	Standard
Licensed, commercially available multichamber bag with additions made in a compounding unit for a specific patient	Tailored, bespoke
Unlicensed compounded formulation made from individual components to a fixed formula	Tailored, bespoke, scratch

The value of licensed multichambered bag products as a basis for PN

The MHRA has clear guidance on the use of 'pharmacy preparations' in its guidance note 14 on unlicensed medicines.[15]

3.1 Pharmaceutical equivalents on the national market Pharmacy preparation are not advisable if a suitable pharmaceutical equivalent with a marketing authorisation is available. Before preparation, the pharmacist should verify whether a pharmaceutical equivalent is available on the national market, taking into consideration the pharmaceutical form and the strength.

Even in a highly regulated and controlled pharmacy environment, the use of multichambered bags has shown to reduce errors by 80% when compared to compounded bags.[14]

A large data analysis in the US revealed that patients receiving an multichambered bag had a lower incidence of blood stream infections than those receiving compounded bags.

Does one size fit all?

No-one has ever claimed that one size of PN solution could be suitable for all patients. Multichambered bags are available in a wide range of nutrition dose, volume and electrolyte options, licensed for use in adults and children. With the right range of standardised solutions aligned to the needs of the local patient cohort a standardised approach can be effective to reduce waste, reduce prescribing errors, improve supply efficiency and simplify purchasing.

This releases resource to closely manage the few patients where the benefit of patient specific compounded solutions outweighs the risks.[16]

Table 2: Comparison of PN Products

	Quality control and compounding risk	Sterility assurance	Stability/ shelf-life	Compatibility	Clinical utility	Cost*
Licensed, commercially available multichamber bag	Content guaranteed.	Guaranteed	18-24 months	N/A	Limited to patients who can have micronutrients via another route or lumen.	Low
Licensed, commercially available multichamber bag with additions made in batch in a licensed compounding unit to a standardised fixed formula	Content assured, some ingredient concentrations may be tested before release depending on supplier. Template order entry mitigates some risks. Risks associated with aseptic manipulation.	Assured, risk dependant on number of additions and environment. Sterility testing may be undertaken.	4 weeks to 3 months.	MCB parameters are fixed, stability matrix more robust.	Suitable for most patients.	Moderate
Unlicensed compounded formulation made from individual components to a fixed formula	Assured, some ingredient concentrations may be tested before release. Template order entry mitigates some risks. Risks associated with aseptic manipulation. Automated compounding may reduce errors when compared to manual compounding.	Assured, risk dependent on operator and environment. Sterility testing may be undertaken.	1 week to 3 months depending on composition, with or without micronutrients, and bag type, e.g. EVA, or oxygen barrier.	Data based on matrix design, higher degree of uncertainty.	Suitable for most patients.	Moderate
Licensed, commercially available multichamber bag with additions made individually in a compounding unit for a specific patient	Assured, some ingredient concentrations may be tested before release. Individualised order entry may increase risk or error. Risks associated with aseptic manipulation.	Assured, risk dependant on number of additions and environment. Sterility testing unlikely as usually made for immediate use.	7 days. An overwrap may need to be applied to permit a longer shelf-life.	MCB parameters are fixed, stability matrix more robust.	Suitable for most patients.	Moderate
Unlicensed compounded formulation made from individual components to a patient specific formulation	Assured, some ingredient concentrations may be tested before release. Individualised order entry may increase risk or error. Risks associated with aseptic manipulation. Automated compounding may reduce errors when compared to manual compounding.	Assured, risk dependant on number of additions and environment. Sterility testing unlikely as usually made for immediate use.	3-89 days depending on composition and bag type, e.g. EVA, or oxygen barrier.	Data based on matrix design, higher degree of uncertainty.	Suitable for most patients.	High

*Considering product acquisition costs and associate resource use.

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