B BRAUN

APPLICANT'S RESPONSE DOCUMENT

to questions listed in the Request for Further Information raised by Health Sciences Authority in Malaysia dated 07.02.2024

The details are as follows:

Procedure	New registration
Application Number	

Medicinal Product concerned	NUTRIFLEX OMEGA PERI NOVO EMULSION FOR INFUSION
ATC code	B05BA10
Pharmaceutical form and strength(s)	Emulsion for infusion

Applicant	B. Braun Medical Industries Sdn. Bhd. (Company Reg: 197401001922 (19051-M) Registered Office: B. Braun 8, No 140 Lebuh Sungai Tiram 1, Taman Perindustrian Bebas Bayan Lepas Fasa 2, 11900 Bayan Lepas, Pulau Pinang, Malaysia. Correspondence Address: P.O Box 880, 10810 Pulau Pinang, Malaysia.
Contact Person authorised for communication (if applicable)	Mei Mei Cheah Asst Manager - Regulatory Affairs Tel: +6046323839 Fax: +604-6433750 B. Braun Medical Industries Sdn. Bhd. (Company Reg: 197401001922 (19051-M))

Question

A7-Indication:

Please provide reference for this statement: Nutriflex® Omega Peri Novo Emulsion for Infusion is indicated in adults, adolescents and children older than two years.

Response

The applicant provides Clinical overview and corresponding literature. Please see page 60-88 in the Clinical Overview.

Question

A8-Recommended Dose:

Please provide the supporting document in section E14 for the pediatric population.

Response

The applicant provides Clinical overview and corresponding literature. Main reference: 'van Goudoever JB, Carnielli V, Darmaun D, Sainz de Pipaon M; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids. Clin Nutr. 2018 Dec;37(6 Pt B):2315-2323.'

Question

A11-Warnings and Precautions:

Please provide supporting document in section E14 for this statement:
Guidelines for parenteral nutrition recommend a daily supply of 60 – 150 mmol (1.0 – 1.5 mmol/kg/d) of sodium. Nutriflex® Omega Peri Novo Emulsion for Infusion provides between 50 to 100 mmol of sodium. Thus, the product provides sufficient amounts of sodium in good agreement with the sodium recommendation for parenteral nutrition.

Response

The applicant provides Clinical overview and corresponding literature. Please see page 55 of the Clinical Overview. Main reference: Biesalski HK, Bischoff SC, Boehles HJ, Muehlhoefer A, Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine. Water, electrolytes, vitamins and trace elements – Guidelines on Parenteral Nutrition, Chapter 7. Ger Med Sci 2009;7 [7 pages].

Question

D1-Inner carton label:

1. Please declare source of ingredients derived from animal origin. (Mei Mei to declare only in the system)

2. Please include the in-use storage condition (already available - no action needed)

3. Observed that electrolytes, calories, osmolality and pH information are included. Please provide supporting document to justify the amount provided are correct.

Response

1. Omega-3-acid triglycerides: Fish species of families like Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae and Scombridae. Esterification of marine oil with ethanol/sodium etoxide in ethanol solution followed by other processing steps. Egg phospholipids: Egg yolk from hens of German origin . LoD is provided,
2. No action necessary . LoD is provided

3. Please refer to the following calculations:

Calculation of Molar Composition

					Label Information			
					1000 mL	Bag volume: 2500 mL	Bag volume: 1875 mL	Bag volume: 1250 mL
Electrolytes (E)	E in Salts / Amino Acids	Molar Mass (g/mol)	Content (g/L)	Molarity Electrolytes (mmol/L)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)
Sodium	NaH2PO4 2*H2O	156,02	0,936	5,999	40	100	75	50
	NaOH	40,00	0,640	16,000				
	NaCl	58,44	0,865	14,802				
	Na(CH3COO) 3*H2O	136,08	0,435	3,197				
Potassium	K(CH3COO)	98,15	2,354	23,984	24	60	45	30
Magnesium	Mg(CH3COO)2 4*H2O	214,46	0,515	2,401	2,4	6,0	4,5	3,0
Calcium	CaCl2 2*H2O	147,02	0,353	2,401	2,4	6,0	4,5	3,0
Zinc	Zn(CH3COO)2	219,50	0,00528	0,024	0,024	0,06	0,045	0,03
Chloride	Lysine HCl	182,65	2,272	12,439	38	96	72	48
	Histidine HCl H2O	209,63	1,352	6,449				
	NaCl	58,44	0,865	14,802				
	CaCl2 2*H2O	147,02	0,353	4,802				
Acetate	Zn(CH3COO)2	219,50	0,00528	0,0481	32	80	60	40
	Na(CH3COO) 3*H2O	136,08	0,435	3,197				
	K(CH3COO)	98,15	2,354	23,984				
	Mg(CH3COO)2 4*H2O	214,46	0,515	4,803				
Phosphate	NaH2PO4 2*H2O	156,02	0,936	5,999	6,0	15,0	11,25	7,5

Calculation Formula:

Molarity Electrolytes [mmol/L) = (Content [g/L] / Molar Mass [g/mol]) x 1000
Example NaH2PO4 * H2O: (0,936 g/L / 156,02 g/mol) x 1000 = 5,999 mmol / L

Sum of Electrolytes [mmol] = Molarity Electrolytes [mmol/L] x volume
Example **Sodium**: 5,999 mmol/L + 16,000 mmol/L + 14,802 mmol/L + 3,197 mmol/L = 39,998 mmol/L
= 40 mmol/L

For 2500 mL = 40 mmol/L x 2,5 = 100 mmol/L
For 1875 mL = 40 mmol/L x 1,875 = 75 mmol/L
For 1250 mL = 40 mmol/L x 1,25 = 50 mmol/L

Calculation of Energy (caloric values for amino acid, glucose and lipids)

Following approx. values are stated on the label for Nutriflex Omega Peri

Compartment		**1250 mL Bag**	**1875 ml Bag**	**2500 mL Bag**
Amino	kcal	**160**	240	320
Glucose	kcal	**320**	480	640
Lipids	kcal	**475**	715	950
Total caloric values	kcal	**955**	1435	1910

The calculations for the caloric values are mainly based on literature known values or theoretical assumptions, specifically for nature-based ingredients like fatty acids.

Calculations for Amino Compartment:

Amount of amino acids per Liter: 80 g/L

Volume of amino acid solution per Bag: 500 mL / 750 mL / 1000 mL

Caloric value for Amino acids solutions: 4 kcal / g[1]

Caloric value calculated (example 1250 mL bag with 500 mL amino acid solution):

In 500 mL Amino Acid Solution are 40 g amino acids, thus, approx. **160 kcal** are supplied with the 1250 mL bag.

Calculations for Glucose Compartment:

Amount of glucose per Liter: 160.02 g/L (based on glucose without monohydrate)

Volume of glucose solution per Bag: 500 mL / 750 mL / 1000 mL

Caloric value for Glucose solutions: 4 kcal / g[2]

Caloric value calculated (example 1250 mL bag with 500 mL glucose solution):

In 500 mL Glucose Solution are 80 g glucose, thus, approx. **320 kcal** are supplied with the 1250 mL bag.

[1] M E May, J O Hill, The American Journal of Clinical Nutrition, Volume 52, Issue 5, November 1990, Pages 770–776
[2] Jeevanandam, 1995; Bolder et al., 2009; Butte et al., 2014

Calculations for Lipids Compartment:

Volume of lipid emulsion per Bag: 250 mL / 375 mL / 500 mL

The caloric values are calculated with literature-based assumptions for the ingredients of the fat emulsion[3]:

MCT: 100 g/L x 8,3 kcal/g = 830 kcal/L

LCT: 80 g/L x 9,2 kcal/g = 736 kcal/L

Omega-3-acid triglycerides: 20 g/L x 10 kcal/g x 0.8 = 160 kcal/L (based on approx. 80% fatty acids are contributing)

Glycerol: 25 g/L x 4,3 kcal/g = 108 kcal/L

Egg Phospholipids for Injection: 12 g/L x 9,2 kcal/g x 0.67 = 74 kcal/L (based on approx. 2/3 of phospholipids are contributing)

Sodium Oleate: 0,3 g/L x 9,2 kcal/g = 3 kcal/L

Alpha-Tocopherol: 0,2 g/L x 7,1 kcal/g = 1 kcal/L

Total of kcal/L rounded to the nearest 5: 1910 kcal/L

Caloric value calculated (example 1250 mL bag with 250 mL lipid emulsion):

1910 kcal/L x 0,25 L = **475 kcal** (rounded to the nearest 5)

Calculations for total caloric value (example 1250 mL bag):

Caloric value for amino acid solution: 160 kcal

Caloric value for glucose solution: 320 kcal

Caloric value for lipid emulsion: 475 kcal

Total: **955 kcal**

[3] Johnson RC, Cotter R. Metabolism of medium-chain triglyceride lipid emulsion. Nutr Int 1986 May/Jun;2(3):150-8. Mirtallo JM. Parenteral formulas. In: Rombeau JL, Rolandelli RH, editors. Clinical nutrition: parenteral nutrition. Third ed. Philadelphia. PA: W. B. Saunders Company; 2001. p. 118-39.

Calculation of Osmolarity					
Amino Acids	Content [g/l]	MW [g/mol]	Content [mol/l]	Amount of Ions	Ions [mol/l]
Isoleucine	4,68	131,17	0,036	1	0,036
Leucine	6,26	131,17	0,048	1	0,048
Lysine HCl	5,68	182,65	0,031	3	0,093
Methionine	3,92	149,21	0,026	1	0,026
Phenylalanine	7,02	165,19	0,042	1	0,042
Threonine	3,64	119,12	0,031	1	0,031
Tryptophan	1,14	204,22	0,006	1	0,006
Valine	5,2	117,15	0,044	1	0,044
Arginine	5,4	174,2	0,031	1	0,031
Histidine HCl*H2O	3,38	209,63	0,016	3	0,048
Alanine	9,7	89,09	0,109	1	0,109
Glycine	3,3	75,07	0,044	1	0,044
Aspartic Acid	3	133,1	0,023	1	0,023
Glutamic Acid	7	147,13	0,048	1	0,048
Proline	6,8	115,13	0,059	1	0,059
Serine	6	105,09	0,057	1	0,057
Sodium Chloride	2,162	58,44	0,037	2	0,074
Sodium acetate * 3 H2O	1,088	136,08	0,008	2	0,016
Potassium acetate	5,886	98,15	0,060	2	0,120
Magnesium acetate * 4 H2O	1,288	214,45	0,006	3	0,018
Calcium chloride * 2 H2O	0,882	147,01	0,006	3	0,018
Sodium hydroxide	1,6	40	0,040	2	0,080
Citric acid * H2O	0,42	210,14	0,002	1	0,002
				theor. Osmolarity [mOsmol/l]	
					1072,4
Glucose	Content [g/l]	MW [g/mol]	Content [mol/l]	Amount of Ions	Ions [mol/l]
Glucose monohydrate	176	198,17	0,888	1	0,888
Sodium dihydrogen phosphate * 2 H2O	2,345	156	0,015	2	0,030
Zinc acetate * 2 H2O	0,0132	201,48	0,000	3	0,000
Citric acid * H2O	0,42	210,14	0,002	1	0,002
				theor. Osmolarity [mOsmol/l]	
					920,4
Lipid	Content [g/l]	MW [g/mol]	Content [mol/l]	Amount of Ions	Ions [mol/l]
Medium-chain triglycerides	100,00	503,00			
Soya bean oil	80,00	856,00			
Egg yolk phospholipids (Egg Lecithin)	12,00	775,00			
Omega-3-acid-triglycerides	20,00	872,00			
α-Tocopherol	0,20	430,71			
Glycerol	25,00	92,09	0,271	1	0,27147
Sodium oleate	0,30	304,44	0,001	2	0,00197
Sodium hydroxide	0,06	40,00	0,002	2	0,00300
WFI	753,50	18,00			
				theor. Osmolarity [mOsmol/l]	
					208,3
Mixture				theor. Osmolarity [mOsmol/l]	
Proportional volume of Amino Acids	0,4				838,78
Proportional volume of Glucose	0,4			round	840
Proportional volume of Lipids	0,2				

Calculation Formula

Content [mol/L] = Content [g/L] / MW [g/mol]
Example (Isoleucine)
4,68 g/L / 131,17 g/mol = 0,036 mol/L

Ions [mol/L] = Content [mol/L] x Amount of Ions
Example (Isoleucine)
0,036 mol/L x 1 = 0,036 mol/L

Theoretical Osmolarity [mOsmol/L] = Sum of Ions [mol/L] in each of the three chambers (Amino, Glucose, Lipid)

Total amount is calculated based on the proportional volumes of the three chambers. This results by round up to 840 mOsmol/L.

pH Limit

The pH limit of 5.0 to 6.0 stated in the texts is following P5.1 and the implemented release and shelf life limits for the read-to-use mixture.

Question

D2-Outer carton label:

1. Please provide the outer carton label for 1250ml
2. Please declare source of ingredients derived from animal origin.
3. Please include the in-use storage condition
4. Please clarify what does PL 03551/0145 PA 0736/033/002, REF 363 6102N mean

Response

1 . The applicant provides again the outer carton label for 1250 ml

2. The applicant is provided a LoD to state that no information will be added on the Label

3. The applicant is provided a LoD to state that no information will be added on the Label

4. Exemples of Label provided are from UK and *PL 03551/0145 PA 0736/033/002, REF 363 6102N is reference specific to UK.*

Question

D3-Package Insert / DFU:

1. Please amend the package insert as per revised in Section A. Please ensure all information is consistent with section A.
2. Please put a space after Infusion for the sentence: "Nutriflex® Omega Peri Novo Emulsion for Infusionshould not be given simultaneously with blood".
3. Please put a space after Infusion for the sentence: "It is recommended that Nutriflex® Omega Peri Novo Emulsion for Infusionbe administered continuously."
4. Kindly ensure the package insert is presented appropriately and readable. Please declare the font size at the bottom of PI (suggested font size min size: 7, as measure in Times New Roman).
5. Please update date of revision and submit the revised package insert for evaluation.

Response

The applicant provides updated DFU and Mock-ups

Question

B2-BMF

1. Please clarify if there is any overfill involved. If yes, please provide overfill justification.

2. Please provide the calculations for the equivalency amount of Lysine, Histidine, Citric Acid and Anhydrous Glucose.

3. Please clarify why the nitrogen is not listed in the formulation for Ready-to-use. Please amend accordingly

Response

1. The filling volume is checked during manufacturing by Process Controls and therefore the correct filling is ensured. Due to different reasons the theoretical yield of 100% cannot be reached during manufacturing. In general, the balancing concept of the electronic batch record allows no consideration of the sampling of bags for chemical, microbiological and process control measurements. Another influence for the calculation of the yield is the average filling volume (out of the batch) which is used for the yield calculation in the EBR. The actual filling volume corresponds to required "overfilling" as described in the method of preparation, in order to achieve the extractable volume.

Furthermore, the technically related solution loss occurred due to, for example: Flushing filters, flushing of pipes and filling machine, solution loss for microbiological sampling, residual volume of solution in filling pipe, is not separately listed in the EBR.

For these reasons and due to increased sampling during the process validation, a compensation calculation for yield is prepared to consider all influences for solution loss during the manufacturing of the process validation batches.

However, it has to be taken into account that slight variations in the estimation of the yield occurred, resulting in a yield +/- 100%. This is caused by several calculation steps with rounding effects and using the average filling volume of the different formats per filling order for the calculation.

But at the end, there is no actual volume overfilling of any compartment of the bag, therefore there is also no API overage involved. The filling volume is controlled by calibrated weighing equipment.

2. Please see equivalency calculation for Lysine – Lysine HCl, Histidine – Histidine HCl H2O, Citric acid – Citric acid H2O and Glucose – Glucose H2O.

Declared

Amounts for AMINO ACID COMPARTMENT & BATCH SIZE:

Starting material	Amount per 1ml (mg)	Amount per 1000ml (g)	Amount per minimum batch size of 6000L (kg)	Amount per maximum batch size of 13600L (kg)	Observation
Lysine HCl	5.680	5.680	34.08	77.25	API

(equivalent to lysine 4.546g)					
Histidine HCl H2O (equivalent to histidine 2.502g)	3.380	3.380	20.28	45.97	API
Citric acid H2O (equivalent to citric acid 0.154 - 0.384g / L)	0.168 - 0.420	0.168 - 0.420	1.008 - 2.520	2.285 - 5.712	Excipient

Amounts for GLUCOSE COMPARTMENT & BATCH SIZE:

Starting material	**Amount per 1ml (mg)**	**Amount per 1000ml (g)**	**Amount per minimum batch size of 6000L (kg)**	**Amount per maximum batch size of 13600L (kg)**	**Observation**
Glucose H2O (equivalent to anhydrous glucose 160.0g)	176.0	176.0	1056	2394	API
Citric acid H2O (equivalent to citric acid 0.154 - 0.384g / L)	0.168 - 0.420	0.168 - 0.420	1.008 - 2.520	2.285 - 5.712	Excipient

Amounts in the READY TO USE mixture for marketed bag volumes, calculations based on the amount per compartment

Starting material	**Amount per 1ml (mg)**	**Amount per 1000ml (g)**	**Amount per bag size of 1250ml (g)**	**Amount per bag size of 1875ml (g)**	**Amount per bag size of 2500ml (g)**	**Observation**
Lysine HCl (equivalent to lysine)	2.272 (1.818)	2.272 (1.818)	2.840 (2.273)	4.260 (3.410)	5.680 (4.546)	API
Histidine HCl H2O (equivalent to histidine)	1.352 (1.000)	1.352 (1.000)	1.690 (1.251)	2.535 (1.876)	3.380 (2.502)	API
Glucose H2O (equivalent to anhydrous glucose)	70.40 (64.00)	70.40 (64.00)	88.00 (80.00)	132.00 (120.00)	176.00 (160.00)	API
Citric acid H2O (equivalent to citric acid)	0.134 – 0.336 (0.123 – 0.307)	0.134 – 0.336 (0.123 – 0.307)	0.168 – 0.420 (0.154 – 0.384)	0.252 – 0.630 (0.231 – 0.576)	0.336 – 0.840 (0.308 – 0.768)	Excipient

Calculation

Starting material	**Molecular weight**	**Starting material**	**Molecular weight**
Lysine	146	Lysine HCl	182.42
Histidine	155	Histidine HCl H2O	209.42
Glucose	180	Glucose H2O	198

Citric acid	192	Citric acid H2O	210

Amounts for AMINO ACID COMPARTMENT & BATCH SIZE

Starting material	**Amount per 1ml (mg)**	**Amount per 1000ml (g)**	**Amount per minimum batch size of 6000L (kg)**	**Amount per maximum batch size of 13600L (kg)**	**Observation**
Lysine HCl (equivalent to lysine 4.546g)	5.680	5.680	34.08	77.25	API
Lysine	(5.680 x 146):182.42 = 4.546	(5.680 x 146):182.42 = 4.546	(34.08 x 146):182.42 = 27.276	(77.25 x 146):182.42 = 61.827	equivalent
Histidine HCl H2O (equivalent to histidine 2.502g)	3.380	3.380	20.28	45.97	API
Histidine	(3.380 x 155):209.42 = 2.502	(3.380 x 155):209.42 = 2.502	(20.28 x 155):209.42 = 15.010	(45.97 x 155):209.42 = 34.024	equivalent
Citric acid H2O (equivalent to citric acid 0.154 - 0.384g / L)	0.168 - 0.420	0.168 - 0.420	1.008 - 2.520	2.285 - 5.712	Excipient
Citric acid	(0.168 x 192):210 to (0.420 x 192):210 = 0.154 to 0.384	(0.168 x 192):210 to (0.420 x 192):210 = 0.154 to 0.384	(1.008 x 192):210 to (2.520 x 192):210 = 0.922 to 2.304	(2.285 x 192):210 to (5.712 x 192):210 = 2.089 to 5.222	equivalent

Amounts for GLUCOSE COMPARTMENT & BATCH SIZE:

Starting material	**Amount per 1ml (mg)**	**Amount per 1000ml (g)**	**Amount per minimum batch size of 6000L (kg)**	**Amount per maximum batch size of 13600L (kg)**	**Observation**
Glucose H2O (equivalent to anhydrous glucose 160.0g)	176.0	176.0	1056	2394	API
Glucose	(176 x 180):198 = 160.0	(176 x 180):198 = 160.0	(1056 x 180):198 = 960.0	(2394 x 180):198 = 2176.364	equivalent
Citric acid H2O (equivalent to citric acid 0.154 - 0.384g / L)	0.168 - 0.420	0.168 - 0.420	1.008 - 2.520	2.285 - 5.712	Excipient
Citric acid	(0.168 x 192):210 to (0.420 x 192):210 = 0.154 to 0.384	(0.168 x 192):210 to (0.420 x 192):210 = 0.154 to 0.384	(1.008 x 192):210 to (2.520 x 192):210 = 0.922 to 2.304	(2.285 x 192):210 to (5.712 x 192):210 = 2.089 to 5.222	equivalent

Amounts in the READY TO USE mixture for marketed bag volumes, calculations based on the amount per compartment

Starting material	**Amount per 1ml (mg)**	**Amount per 1000ml (g)**	**Amount per bag size of 1250ml (g)**	**Amount per bag size of 1875ml (g)**	**Amount per bag size of 2500ml (g)**	**Observation**
Lysine HCl* (equivalent to lysine)	2.272 (1.818)	2.272 (1.818)	2.840 (2.273)	4.260 (3.410)	5.680 (4.546)	API
Lysine	(2.272 x 146) / 182.42 = 1.818	(2.272 x 146) / 182.42 = 1.818	(2.840 x 146) / 182.42 = 2.273	(4.260 x 146) / 182.42 = 3.410	(5.680 x 146) / 182.42 = 4.546	equivalent
Histidine HCl H2O (equivalent to histidine)	1.352 (1.000)	1.352 (1.000)	1.690 (1.251)	2.535 (1.876)	3.380 (2.502)	API
Histidine	(1.352 x 155) / 209.42 = 1.000	(1.352 x 155) / 209.42 = 1.000	(1.690 x 155) / 209.42 = 1.251	(2.535 x 155) / 209.42 = 1.876	(3.380 x 155) / 209.42 = 2.502	equivalent
Glucose H2O (equivalent to anhydrous glucose)	70.40 (64.00)	70.40 (64.00)	88.00 (80.00)	132.00 (120.00)	176.00 (160.00)	API
Glucose	(70.40 x 180) / 198 = 64.00	(70.40 x 180) / 198 = 64.00	(88 x 180) / 198 = 80.00	(132 x 180) / 198 = 120.00	(176 x 180) / 198 = 160.00	equivalent
Citric acid H2O (equivalent to citric acid)	0.134 – 0.336 (0.123 – 0.307)	0.134 – 0.336 (0.123 – 0.307)	0.168 – 0.420 (0.154 – 0.384)	0.252 – 0.630 (0.231 – 0.576)	0.336 – 0.840 (0.308 – 0.768)	Excipient
Citric acid	(0.134 – 0.336) x 192/210 = (0.123 – 0.307)	(0.134 – 0.336) x 192/210 = (0.123 – 0.307)	(0.168 – 0.420) x 192/210 = (0.154 – 0.384)	(0.252 – 0.630) x 192/210 = (0.231 – 0.576)	(0.336 – 0.840) x 192/210 = (0.308 – 0.768)	equivalent

***Explanation for the ready-to-use amounts**

Lysine HCl

In 1000 ml aminoacid compartment we have 5.680 g Lysine HCl, then

In 1250 ml ready-to-use emulsion with an aminoacid compartment of 500 ml we have (5.680 x 500):1000 = 2.840 g Lysine HCl, and

In 1875 ml ready-to-use emulsion with an aminoacid compartment of 750 ml we have (5.680 x 750):1000 = 4.260 g Lysine HCl, and

In 2500 ml ready-to-use emulsion with an aminoacid compartment of 1000 ml we have (5.680 x 1000):1000 = 5.680 g Lysine HCl.

And if in 1250 ml ready-to-use emulsion we have 2.840 g Lysine HCl, then

In 1000 ml ready-to-use emulsion we have 2.272 g Lysine HCl, and

In 1 ml ready-to-use emulsion we have 2.272 mg Lysine HCl.

Histidine HCl H2O

In 1000 ml aminoacid compartment we have 3.380 g Histidine HCl H2O, then

In 1250 ml ready-to-use emulsion with an aminoacid compartment of 500 ml we have (3.380 x 500):1000 = 1.690 g Histidine HCl H2O, and

In 1875 ml ready-to-use emulsion with an aminoacid compartment of 750 ml we have (3.380 x 750):1000 = 2.535 g Histidine HCl H2O, and

In 2500 ml ready-to-use emulsion with an aminoacid compartment of 1000 ml we have (3.380 x 1000):1000 = 3.380 g Histidine HCl H2O.

And if in 1250 ml ready-to-use emulsion we have 1.690 g Histidine HCl H2O, then

In 1000 ml ready-to-use emulsion we have 1.352 g Histidine HCl H2O, and

In 1 ml ready-to-use emulsion we have 1.352 mg Histidine HCl H2O.

Glucose H2O

In 1000 ml glucose compartment we have 176 g Glucose H2O, then

In 1250 ml ready-to-use emulsion with a glucose compartment of 500 ml we have (176 x 500):1000 = 88 g Glucose H2O, and

In 1875 ml ready-to-use emulsion with a glucose compartment of 750 ml we have (176 x 750):1000 = 132 g Glucose H2O, and

In 2500 ml ready-to-use emulsion with a glucose compartment of 1000 ml we have (176 x 1000):1000 = 176 g Glucose H2O.

And if in 1250 ml ready-to-use emulsion we have 88 g Glucose H2O, then

In 1000 ml ready-to-use emulsion we have 70.40 g Glucose H2O, and

In 1 ml ready-to-use emulsion we have 70.40 mg Glucose H2O.

Citric acid H2O

In 1000 ml glucose compartment and 1000 ml amino acid compartment we have 2 x (0.168 – 0.420) g Citric acid H2O, then

In 1250 ml ready-to-use emulsion with a glucose compartment of 500 ml and an amino acid compartment of 500 ml we have (0.336 - 0.840) x 1000/2000 = 0.168 – 0.420 g Citric acid H2O, and

In 1875 ml ready-to-use emulsion with a glucose compartment of 750 ml and an amino acid compartment of 750 ml we have (0.336 - 0.840) x 1500/2000 = 0.252 – 0.630 g Citric acid H2O, and

In 2500 ml ready-to-use emulsion with a glucose compartment of 1000 ml and an amino acid compartment of 1000 ml we have (0.336 - 0.840) x 2000/2000 = 0.336 – 0.840 g Citric acid H2O.

And if in 1250 ml ready-to-use emulsion we have 0.168 – 0.420 g Citric acid H2O, then

In 1000 ml ready-to-use emulsion we have 0.134 – 0.336 g Citric acid H2O, and

In 1 ml ready-to-use emulsion we have 0.134 – 0.336 mg Citric acid H2O.

3. In regard to the clarification why the nitrogen is not listed in the formulation for Ready-to-use emulsion, B. Braun Melsungen AG wishes to state the following:

- Nitrogen as a filtered gas is used before the beginning of preparation of the aminoacid and glucose solutions, for reducing by purging the oxygen content in the vessels;

- As of the ICH Q8(R2) Guideline, Current Step 4 version, dated August 2009, even if a substance / an excipient may not be present in the final product but served in the manufacture of the product, it should be discussed in the contents of Section *Pharmaceutical Development* for drug products. Therefore, Sections should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids). Therefore, in already submitted document "Batch Formula", Nitrogen is listed as a processing aid, for the preparation of the amino acid and glucose solutions.

In the proposed SmPC of the product, the applicant is not listing Nitrogen in the list of Excipients (section *6.1 List of excipients*), as this gas is no longer present in the finished product (i.e., contents of the amino acid and glucose chambers), which is applied to the patient.

- The Nitrogen content, listed in the proposed SmPC under section *2. QUALITATIVE AND QUANTITATIVE COMPOSITION*, is referring exclusively to the nitrogen coming from the -amino groups present in the chemical structure of the amino acids. This information is not connected to the processing aid and gas nitrogen used during manufacturing process.

Question

E7: Other manufacturers

Please clarify if there is any other manufacturer involved in the finished product.

Response

Please see Letter of Declaration.

Question

E12: Analytical method

1. Please provide the POA for Assay, dihydrogenphosphate
2. Please provide the calculation for assay zinc. (submit appendix with calculation)
3. BET: Please provide MVD calculation
4. Please clarify which BET method is used routinely, Method A or D?
5. Kindly ensure PoA is standardized with specifications listed in Section P5.1

Response

1. Please see attached to this response the Test Procedure for phosphate. Please note that from a simplification point of view, the applicant is referring both to phosphate or dihydrogenphosphate but there is only one parameter tested and corresponding test procedure - TP 74207-36e-R. This

Test Procedure is used for the determination of phosphate or dihydrogenphosphate. The content of phosphate (in mmol/l) corresponds to the content of dihydrogenphosphate (in mmol/l).

2. *Calculation for Zn^{2+} according TP-74130-31*:

The calculation of the final results is based on a four-point calibration (three standard levels and a non-spiked blank) with quadratic calibration function. The measured signal is converted into a corresponding concentration using the calibration function. In dependence of the required unit, the concentration is converted from mg/l to mmol/l. The entire calculation is carried out automatically by the analysis software.

Example: $y = ax^2 + bx + c$, $x = \frac{-b \pm \sqrt{b^2 - 4a(c-y)}}{2a}$

Calibration function: y = -0,023249x² + 0,42056x - 0,0014
measured Signal (y) = 0.206 A
Dilution factor = 20
Molar mass for Zn: 65.39 [g/mol]
x = zinc concentration [mg/l]

$$x = \frac{-0.42056 + \sqrt{0.42056^2 - 4 * (-0.023249) * (-0.0014 - 0.206)}}{2 * (-0.023249)}$$

x = 0.507 [mg/L]

$$x\ \left[\frac{mmol}{l}\right] = \frac{0.507\left[\frac{mg}{l}\right] * 20}{65.39\ \left[\frac{g}{mol}\right]} = 0.155\ mmol/l$$

3. The determination of the MAXIMUM VALID DILUTION (MVD) is done according to Monography BACTERIAL ENDOTOXINS TEST from the US Pharmacopoeia (please see it attached to this response letter). The maximum valid dilution is the maximum allowable dilution of a specimen at which the endotoxin limit can be determined.

The corresponding equation is:

MVD = (endotoxin limit × concentration of Sample Solution) / (λ)

The endotoxin limit for parenteral drugs, defined on the basis of dose, equals K/M, where K is a threshold pyrogenic dose of endotoxin per kg of body weight, and M is equal to the maximum recommended bolus dose of product per kg of body weight. When the product is to be injected at frequent intervals or infused continuously, M is the maximum total dose administered in a single hour period. The endotoxin limit for parenteral drugs is specified in the individual monograph in units such as EU/mL, EU/mg, EU/Unit of biological activity, etc.

Concentration of Sample Solution

mg/mL: in the case of endotoxin limit specified by weight (EU/mg); Units/mL: in the case of endotoxin limit specified by unit of biological activity (EU/Unit); mL/mL: when the endotoxin limit is specified by volume (EU/mL).

λ: the labeled sensitivity in the Gel-Clot Technique (EU/mL) or the lowest concentration used in the standard curve for the Turbidimetric Technique or Chromogenic Technique.

Calculation for sol. no. 0739:

Endotoxin limit = ≤ 2,0 EU/mL
Concentration of sample solution = 1
Lysate sensitivity λ = 0,005 EU/mL
MVD = 2,0 EU/mL x 1 / 0,005 EU/mL = 400
MVD is dilution 1:400, validated routine analysis is 1:100

4. The applicant would like to clarify that for Bacterial Endotoxin Testing Method D is the most used method but Method A is also used as a back-up method.

5. The Procedure of Analysis (Test Procedures) are standardized with specifications listed in Section P5.1.

Question

E13: Validation of Analytical Method

1. Determination of Calcium in amino acid solution by Atomic Absorption Spectrometry (acc. to TP 74109-31e) : Please provide the results for Specificity
2. Assay Determination of DL-alpha-tocopherol in fat emulsions by HPLC (acc. to TP 74407-46e draft) (Non Compendial): Please provide the results for ~~Specificity~~ System suit, initial validation VBA-2445-01
3. Assay Validation of Quantitative Analysis of Glycerol by GC-FID (TP 74D57-44, V4.0) (Non Compendial): Please provide the results for ~~Specificity~~ System suitability
4. Sterility (Validation of the Test for Sterility of Nutriflex® Omega Peri Novo Emulsion for Infusion) (Compendial): The data in E12 is incomplete. Please provide analytical method validation specific for Sterility Test and its validation result specific for this product.
5. BET (Validation of the test for bacterial endotoxins of Nutriflex® Omega Peri Novo Emulsion according to the chromogenic kinetic method (Method D)) (Compendial): Please provide the confirmation of lysate sensitivity documents in English. The data in E12 is incomplete. Please provide analytical method validation for Bacterial Endotoxin Test and its validation result specific for this product. Kindly attach at respective section at section E13 under category BET.
Please include the calculation of MVD.

6. BET (Validation of the test for bacterial endotoxins of Nutriflex® Omega Peri Novo Emulsion according to the chromogenic kinetic method (Method A)) (Compendial): Please clarify which BET method is used routinely, Method A or D?
7. Assay Determination of Acetate and L-Pyroglutamic acid in Nutriflex aqueous solutions (acc. to TP 74A34-46) (Non Compendial) - please provide system suitability

Response

1. Specificity/selectivity was demonstrated by injection of blank solution and unspiked worst case matrix.

Specificity/Selectivity (Punkt 6.2.11) ✓

Level	Best. Nr.	gefundene Konzentration Ca [µmol/L]
Blank	1	-0.1044 ✓
	2	-0.0756 ✓
	3	0.0068 ✓
Matrix	1	-0.0090 ✓
	2	0.1329 ✓
	3	-0.0092 ✓

Calcium is measured at a wavelength of 422.7 nm corresponding to the transition of highest intensity in neutral calcium ((from 4s2 (1S0) to 4s4p (1Po1), cf. "Handbook of Basic Atomic Spectroscopy", DOI 10.1063/1.1800011). Therefore, specificity (selectivity) was demonstrated additionally by meeting the accuracy requirements. In summary, specificity/selectivity was successfully validated.

2.System suitability report is provided from recent routine analysis, additional to this response letter. Please see method specificity details and chromatograms in document "Determination of DL-alpha-tocopherol in B.Braun product numbers 170, 179, 739, 740 and 418 by HPLC (acc. to TP 74407-46e draft)" - section *6.2.12 Specificity/selectivity (pages 26-37/60).* Additionally, the applicant is providing document VBA-2445-01, as requested, which document summarizes the validation activities which were performed to demonstrate suitability of the test procedure.

3. System suitability report is provided from recent routine analysis, additional to this response letter. Please see method specificity details and chromatograms in document "Validation of "Quantitative Analysis of Glycerol by GC-FID "(TP 74D57-44, V4.0)" – section *5.6 Specificity/selectivity (pages 34-45/59).*

4. The applicant is providing document Validierung der Prüfung auf Sterilität Nutriflex Omega peri (739) (inklusive Rohdaten), referring to the analytical method validation specific for Sterility Test and its validation result specific for this product.

5. The applicant is submitting document BERICHT - Validierung des Tests auf bakterielle Endotoxine in Lösungen und Emulsionen mittels chromogen kinetischer Methode D, Lösung 739, Nutriflex omega peri (VAL-P-MEG-009783) for the validation of Method D, which document is product specific and additionally is providing the confirmation of lysate sensitivity documents in English.

6. The applicant would like to clarify that for Bacterial Endotoxin Testing Method D is the most used method but Method A is also used as a back-up method.

7. Please see system suitability test described in document "TP-74A34-46-R_Determination of Acetate and L-Pyroglutamic acid in amino acid solutions" – *4.3. System suitability test(pages* 4-5/8). System suitability report is provided from recent routine analysis, additional to this response letter.

Question

P3.4-Process validation/evaluation

1) Referring to the file named '' p34-proc-val-3-ValReport.pdf'' pdf page 12/85 and 13/85, please provide the validation plan VP2272-01 and VAL-P-MEG-5-002418.
2) Referring to the file named '' p34-proc-val-3-ValReport.pdf'' pdf page 13/85 ,it is stated chemical finished product analysis for batches with 2 bag formats were performed once in the beginning, one or two times in the middle (depending on the filling batch size; defined in annex 10 and annex 12 to process validation protocol). Please provide the complete process validation protocol.
3) Referring to the file named '' ' p34-proc-val-3-ValReport.pdf'' pdf page 13/85, it is stated details are defined in validation and test matrix for Nutriflex II. Additionally, the inter and intra batch homogeneity of the products were considered in the process validation (see Annex 05 to VB-2272-01 Homogeneity of production Nutriflex II (VAL-P-MEG-5-002802). Please provide annex 05 (Doc-ID:VAL-P-MEG-5-002802).
4) Please provide the PV report for the PV protocol (VP-3955-01) for evaluation

Response

The Applicant provides an update to P.3.4, with the following documents:

- VP-2272-01: Process Validation of Nutriflex product group produced in Life Nutrition - Question 1 (please see Validation Plan at page 47) and Question 2 (please see entire document)
- Document VAL-P-MEG-5-002418: Validierungsmatrix Nutriflex II Annex 2 zu VMP-097 (Question 1).
- Annexes 10 and 12 to Process Validation Nutriflex II product group (VP-2272-01) Microbiological analytics filling unsterile product (Question 2).
- Annex 5 to VB-2272-01 Process Validation Nutriflex II product group Homogeneity (Question 3).
- Report Process Validation Solution 739 Nutriflex II for International Registration (VB-3995-01), for already submitted protocol VP-3995-01.

Question

P5.1: Finished Product Specification

1. Please provide the calculation for the BET

2. Please provide the reference of 5-Hydroxymethylfurfural, Mean particle diameter (PCS), Peroxide value, Acid value, Free Fatty Acids.
3. Please include water loss testing for shelf life as part of the specification

Response

1. The calculation for the BET limit is done according to methods A & D in Ph. Eur. Monography *Bacterial endotoxins (2.6.14)*. Please find the monography and the calculation attached to this response letter. The exact calculation is done via WinKQCL software, because the limit, the lysate sensitivity (smallest standard) and the dilution are entered as inputs. If the dilution is too high so the MVD is exceeded, the software gives a warning.

2. Please find attached to this response letter the References of the Method for the test procedures for 5-Hydroxymethylfurfural, Mean particle diameter (PCS), Peroxide value, Acid value, Free Fatty Acids.

3. The applicant wishes to clarify that the water loss parameter is tested in the stability studies and clearly shows that there is no significant water loss (<5%) at the end of the shelf-life. The applicant is also mentioning that including this parameter in the Specification of the Finished Product would only create a country specific document and this is set as preferably to be avoided from the regulatory point of view.

Question

P5.4: Batch Analysis / P5.4.1 CoAs of FP

1. Specification & limit: Please refer P5.1 & revise accordingly.
2. Please remove COA for batch no: 224528231 as it is not the same product as per proposed product.
3. Please provide the results in numerical for sub-visible particles, Clarity and degree of opalescence, Microscopic assessment and BET.
4. Please submit a declaration letter to confirm on formulation, packaging material & API manufacturer of COA batches.

Response

1. The Specifications and limits are not changed as a justification is included for the omission of water loss in Section P5.1
2. The CoA is not removed as it is the same product but registered with a different name to other country. The coa is then used for submission here.

3. Please find attached to this response the results in numerical for the requested parameters. The applicant wishes to clarify that the Batch analysis / CoA template is a feature of the software used for issuing these documents and cannot be changed.
4. The applicant is attaching a Letter of Declaration, for confirming the formulation, packaging material & API manufacturer of CoA batches.

P7: Container closure system

1. Please submit specifications and CoAs of primary packaging for 1875 ml and 2500 ml bags.
2. Please submit specifications and control of outer carton (test procedure carried out (i.e.certificate of analysis) if available.
3. Please ensure the documents submitted is consistent throughout the dossier in Section C, P2.5, and P7. If not, please revise according to remarks in respective sections mentioned

Response

1. The applicant is updating the submitted documentation with the specifications and CoAs for 1875 ml and 2500 ml bags. Please find them attached to this response.

2. The applicant is updating the submitted documentation with the specifications of outer carton.

3. 3.The documents submitted here is consistent with information given in Section C, P2.5, and P7. However, please take note that the information in P7 will be a much more detailed one, as compared to the other sections.

Question

P8: Stability

1. Please clarify the BET limit for real time 30 degree Celsius study for both batches stated 2.5 I.U/mL, while the specification in P5.1 is 2.0 I.U/mL. Please clarify.
2. Please update and provide the real-time stability report up to the latest time point (24 months) for batch number: 211068231 and 205658231).

Response

1. The Bacterial endotoxins by means of the LAL test according to Ph.Eur. Method A - limit for 30 degrees Celsius – had a requirement of ≤ 2.5 I.U./ml, according to a version of the Finished Product Specification (always in line with the Ph.Eur) dating before 2019.

The applicant initially validated the analysis for 0739 with method A with a limit of detection of 1,92 I.U/mL, which is below 2,0 and 2,5 I.U./mL and therefore adequate and afterwards with method D with a limit of detection of 2,0 I.U./mL and optimized the analysis to a limit of detection of 0,01 I.U./mL (please see document VAL-P-MEG-009783 - *BERICHT - Validierung des Tests auf bakterielle Endotoxine in Lösungen und Emulsionen mittels chromogen kinetischer Methode D, Lösung 739, Nutriflex omega peri*). The limit was decreased from 2,5 to 2,0 I.U./mL in the Finished Product Specification.
In every case the result was below or identically to 2,0 and 2,5 I.U./mL and therefore adequate.

2. The applicant is updating P8 by providing the corresponding Report, Stability and Water loss data for the two batches of Nutriflex Omega Peri [Novo Emulsion For Infusion].

Question

P8: In-use stability

1. Please declare the packaging materials and API source for in-use stability batches
2. Please declare the storage condition before in-use stability study
3. In document no.: REP-RDP-003838-1-0, the specification for pH is 4.6-6.2. Please clarify the difference in pH specification as per P5.1 which is pH 5-6.
4. Please clarify if batches tested in document REP-RDP-003838-1-0 is the same as the 2 batches tested for chemical stability; REP-RDP-005203-3-0.
5. As per commitment letter, please provide the in-use stability study at end of shelf life, (completed in Q2 2023)

Response

1. Please find attached to this response letter the Letter of Declaration for the packaging materials and API source for in-use stability batches.

2. The Applicant provides an update to P.8 with the report "Stability after Mixing Study of Omegaflex peri (sol. no. 0739), Lipoflex special (sol.no. 0844) and Lipoflex peri (sol.no. 0846)", whereas samples close to shelf life were used. Physicochemical stability of an end of shelf life solution of mixed Nutriflex products (**0739**, 0844 and 0846) is confirmed for 9 days (i.e. 7 days between +2°C and +8°C plus 2 days at room temperature). Please see also point 5 of this response.
For the already submitted report "Additional In-Use Stability Tests on Nutriflex Omega peri and Nutriflex Omega special w/o electrolytes", all parameters tested for in-use stability of Nutriflex Omega peri and Nutriflex Omega special without electrolytes at the beginning of shelf-life are within the defined specification limits directly after mixing and after a storage period of 9 days (7 days between +2°C and +8°C in darkness, 2 days at room temperature and daylight). This is mentioned in pages 1-2/9.
3. The pH specification in the test report REP-RDP-003838 was set to 4.5- 6.2 at the time of testing independent to the pH specification of P5.1 which is pH 5.0 – 6.0. The only relevant pH specification for the in-use testing (stability after mixing) is 5.0 – 6.0. If this specification limit is taken into account, the same final result of this in-use test is given due to the fact that all measured values fulfill the limit of 5.0-6.0 as well.
4. Document **REP-RDP-003838** is referring to In-Use Stability Tests on Nutriflex Omega Peri [Novo] and Nutriflex Omega special w/o electrolytes. The purpose of the in-use stability study is to provide information on storage conditions and stability after aseptic mixing, mimicking a typical routine handling in hospitals. It is performed to evaluate whether the mixed product is stable over a period of 9 days. Therefore the secondary bag was removed, the three chambers were mixed and different parameters were analyzed. After a storage time of 9 days (7 days between +2°C and +8°C in darkness, 2 days at room temperature and daylight) the samples were analyzed again. The Nutriflex Omega Peri [Novo Emulsion For Infusion] studied batch was **1408183535**.

Document **REP-RDP-005203** is referring Chemical stability of Nutriflex Omega Peri [Novo] and Nutriflex Omega special w/o electrolytes during in-use studies. This in-use stability study was performed to evaluate the chemical and physical stability of the mixture of glucose chamber and amino acid chamber at different time points and storage conditions after aseptic mixing. After mixing the samples were stored for 24 h, 36 h, 48 h and 60 h at room temperature (20°C – 25°C) as well as 4 days or 7 days in a refrigerator (+2°C and +8°C) and additional two days at room temperature (20°C – 25°C) and daylight but without direct solar radiation. The Nutriflex Omega Peri [Novo Emulsion For Infusion] studied batches were **164038299 and 164548299**.
Therefore, the above descried two studies included different batches of Nutriflex Omega Peri Novo Emulsion For Infusion.

5. The Applicant provides an update to P.8 with the report "Stability after Mixing Study of Omegaflex peri (sol. no. 0739), Lipoflex special (sol.no. 0844) and Lipoflex peri (sol.no. 0846)", whereas samples close to shelf life were used, as of the Letter of Commitment dated 03-03-2023. Please see also point 1 of this response.