Question

A20: Shelf life

Please finalize once requirement in P8 has been fulfilled. We still require in use stability data which support chemical and physicochemical claimed & cover the infusion time during administration. updated letter along with scientific justification related to the proposed product in order to be considered for the exemption.

Response

The most recent stability data is submitted in section P8. Please find attached to this letter a Letter of Justification and also a scientific justification for the application to shelf-life 24 months / 25°C.A20 has been revised to include '(Before spiking the infusion port)' after the statement 'After removing the protective overwrap and after mixing of contents of the bag.'

Question

D1: Inner carton label

1. For storage condition:
- Please refer remarks in A20.
- As stated in A20: The shelf life claimed has been separated to 3 conditions i.e After removing the protective overwrap and after mixing of contents of the bag, After admixture of compatible additives & After first opening (spiking of the infusion port).
- However, as declared on the label: After first opening and mixing the product: should be used immediately. In A20 shelf life proposed for After first opening & after mixing of contents are different/ separated. Please clarify on the inconsistency. What does it mean by after mixing the product? Does it mean After admixture of compatible additives OR After mixing of contents of the bag?
2. Only calculation of osmolarity was provided in E14. Please provide reference/ calculation on osmolality.

Response

1. The product has a proposed shelf-life of 24 months at 25°C if left unopened (secondary packaging, i.e., overwrap intact).
After mixing the 3 component chambers, it was proven via a scientific study (In-use stability tests on Nutriflex Lipid EU products – please refer to document REP-RDP-003423) that the products will remain physically and chemically stable for 7 days between +2°C and +8°C and 2 additional days at room temperature.
Another scientific study (Physicochemical Stability of Nutriflex Lipid II EU Products Upon Supplementation with miscellaneous additives – please refer to document REP-RDP-003404) proved that after the three chambers of the primary bag were mixed and different additives were aseptically supplemented through the chamber port system in a clean air workbench, the products - (mixed chambers in further admixtures containing additional amino acids in form of N(2)-L-alanyl-L-glutamine, electrolytes, organic or inorganic phosphates, trace elements and vitamins) - are stable for at least 7 days between +2°C and +8°C and 2 additional days at room temperature.
However, the recommendation for this product's use is that it should be administrated immediately after opening (opening the overwrap, mixing the chambers, eventual further admixture with additives). **There is no benefit to the patient in preparing the mixture of the 3 chambers, then the admixtures with the additives, then storing it for several days in different conditions only because the physical - chemical stability of the mixtures / admixtures was proven in the laboratory**. The applicant also wishes to highlight that the main objective is to administer to the patient a product which was handled as less as possible by different persons involved in patient's care and exposed as less as possible to septic environment, different and separate admixture operations, etc. because all these would be possible conditions for microbial contamination of the product.

The statement *'After first opening and mixing the product: should be used immediately.'* is replaced with the shelf life claimed in A20.

2. The applicant wishes to clarify that **Osmolality** is a measure of osmoles of solute per kilogram of solvent (Osm/kg) and the **Osmolarity** is the measure of osmoles of solute per liter of solution (Osm/L).

Please consider that the determination of Osmolality/Osmolarity in the Quality Control laboratory, is done according to the monograph 2.2.35. OSMOLALITY, of the European Pharmacopoeia, therefore according to an instrumental analytical method (measurement of the depression of freezing point with an Osmometer). Please find the monograph attached to this response letter. Please find the monograph attached to this response letter and also the US Pharmacopoeia monograph Osmolality / Osmolarity <785>. The values are measured in the mixtures of the chambers (ready-to-use product).

The measurement of the number of solutes in the solution allows the direct determination of the osmolality of the solution with units of moles of solutes per kilogram of solvent. This osmolality result can be converted into a value for osmolarity with units of moles of solutes per liter of solvent, typically water.
Please also consider that in the SmPC / DfU, there are stated mean (average) values of the Osmolarity / Osmolality – 840 mOsm/L / 950 mOsm/L.
The term **Osmolality** expresses concentrations relative to the mass of the solvent.
Please find below a theoretical calculation based on the ion-formation behaviour of the APIs and excipients in water (the solvent).

Coming from aminoacid chamber	g/l	MW (g/mol)	g/kg water	mol/kg water	Amount of ions	Osm/kg
Isoleucine	4.68	131.17	5	0.038	1	0.038
Leucine	6.26	131.17	6.69	0.051	1	0.051
Lysine HCl	5.68	182.65	6.07	0.033	3	0.099
Methionine	3.92	149.21	4.19	0.028	1	0.028
Phenylalanine	7.02	165.19	7.5	0.045	1	0.045
Threonine	3.64	119.12	3.89	0.033	1	0.033
Tryptophan	1.14	204.22	1.22	0.006	1	0.006

Valine	5.2	117.15	5.55	0.047	1	0.047
Arginine	5.4	174.2	5.77	0.033	1	0.033
(Histidine HCl) H2O	(3.09)3.38	(191.62)209.63	3.3	0.017	3	0.051
Alanine	9.7	89.09	10.36	0.116	1	0.116
Aspartic acid	3	133.1	3.2	0.024	1	0.024
Glutamic acid	7	147.13	7.48	0.051	1	0.051
Glycine	3.3	75.07	3.52	0.046	1	0.046
Proline	6.8	115.13	7.26	0.063	1	0.063
Serine	6	105.09	6.41	0.061	1	0.061
Sodium hydroxide	1.6	40	1.71	0.043	2	0.086
Sodium chloride	2.162	58.44	2.31	0.04	2	0.08
(Sodium acetate) 3H2O	(0.656)1.088	(82.03)136.08	0.7	0.009	2	0.018
Potassium acetate	5.886	98.15	6.29	0.064	2	0.128
(Magnesium acetate) 4H2O	(0.855)1.288	(142.39)214.45	0.91	0.006	3	0.018
(Calcium chloride) 2H2O	(0.666)0.882	(110.98)147.01	0.71	0.006	3	0.018
(Citric acid) H2O	(0.384)0.42	(192.12)210.14	0.41	0.002	1	0.002
						1.142

Water = 935 g + *1.407* (*coming from hydrates*) 0.93641 kg/l

Coming from glucose chamber	**g/l**	**MW (g/mol)**	**g/kg water**	**mol/kg water**	**Amount of ions**	**Osm/kg**
(Glucose) H2O	(160)176	(180.16)198.17	178.26	0.989	1	0.989
(Sodium Dihydrogen Phosphate) 2H2O	(1.804)2.345	(120)156	2.01	0.017	2	0.034

(Zinc Acetate) 2H2O	(0.012)0.0132	(183.48)201.48	0.013	0	3	0
(Citric acid) H2O	(0.384)0.42	(192.12)210.14	0.43	0.002	1	0.002
						1.025

Water = 881 g + *16,578* 0.89758 kg/l

(*coming from hydrates*)

Coming from lipid chamber	**g/l**	**MW (g/mol)**	**g/kg water**	**mol/kg water**	**Amount of ions**	**Osm/kg**
Medium-chain Triglycerides						
Soya-Bean Oil, Refined						
Egg Phospholipids for Injection						
Alpha-tocopherol						
Sodium Oleate	0.06	304.44	0.08	0.0002	2	0.0004
Sodium hydroxide	0.012	40	0.02	0.0005	2	0.001
Glycerol	25	92	33.16	0.36	1	0.36
Water for Injections						
						0.361

No contribution

Water = 753.5 0.7535 kg/l

Total osmolality - mOsm/kg = (1142x0.4) + (1025x0.4) + (361x0.2) ~ 950

Please consider that approximations were made. For example, excipient citric acid (glucose and amino acid chambers) is added in the manufacturing process within a range and the calculations were made with the maximum value of the range. Also, for the calculus, the coefficients (0.4; 0.4; 0.2) were added as the initial values of concentrations (second column, <g/l>) are concentrations of the API/excipient in solution, in the corresponding chamber, and each chamber has a contributive proportion to the final solution. This can be done as the water is the solvent for each of the three chamber's electrolytes.

Question

D2: Outer carton label

1. For storage condition:

- Please refer remarks in A20.

- As stated in A20: The shelf life claimed has been separated to 3 conditions i.e After removing the protective overwrap and after mixing of contents of the bag, After admixture of compatible additives & After first opening (spiking of the infusion port).

- However, as declared on the label: After first opening and mixing the product: should be used immediately. In A20 shelf life proposed for After first opening & after mixing of contents are different/ separated. Please clarify on the inconsistency. What does it mean by after mixing the product? Does it mean After admixture of compatible additives OR After mixing of contents of the bag?

2. Only calculation of osmolarity was provided in E14. Please provide reference/ calculation on osmolality.

Response

1. Please refer to issue ***D1: Inner carton label*** – Question 1, above.
2. Please refer to issue ***D1: Inner carton label*** – Question 2, above.