COMMITTEE PAPER FOR DISCUSSION **ACNFP/150/03**

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

NOVEL FOOD APPLICATION FOR CETYLATED FATTY ACIDS – RP200, FURTHER INFORMATION FOR REVIEW

Issue

An application has been received under the novel food authorisation process (regulation 2015/2283 as repatriated) for cetylated fatty acids.

The Committee is asked to advise on whether the available data provides an adequate basis for a risk assessment, and whether there are safety concerns with the proposed use of this novel food in the UK market.

Background

On the 10th of February 2021, the FSA received the submission for Cetylated Fatty Acids for Pharmaneutra S.p.a.

1. The cetylated fatty acids are produced by reacting cetyl alcohol with myristic acid and oleic acid. The resulting esters (cetylated fatty acids) are then mixed with olive oil. This finished product is intended to be used as an ingredient in food supplements.

2. The application dossier is attached as **Annex C** and annexes to the dossier are attached as **Annexes D, E and F**. All contain confidential information.

EFSA consideration of the novel food

3. In parallel to submitting the application to the UK for assessment the applicant has also submitted an application to EFSA. EFSA have completed their consideration and the EFSA opinion (**Annex G**) is provided to the Committee as further data to inform their assessment.

This application

Identification

4. The novel food is a mixture of 83% cetylated fatty acids and a smaller number of fatty acids and triglycerides. With cetyl myristate being the dominant cetylated fatty acid. The mixture is contained within Olive oil. It is produced from cetyl alcohol (hexadecan-1-ol) and the fatty acids, myristic acid and oleic acid. The composition of the novel food ingredient has been verified by GC-FID.

Production Process

5. Cetylated fatty acids are first synthesised by reacting cetyl alcohol, myristic acid with a zinc catalyst or cetyl alcohol, oleic acid with a zinc catalyst under high heat and vacuum.

6. After cooling, the refined cetylated fatty acids undergo decolourisation, and are then mixed with olive oil under high heat and vacuum. Further deodorisation and filtration of the mixture yields the novel food ingredient.

7. All starting materials and processing aids are reported as food grade. Certificates of analysis for all materials are listed **Annex D** [Annex I Raw Materials and Allergen Statements].

8. Detailed HACCP plan for the production process provided in **Annex D** [Annex II HACCP]. This has identified the key steps in the process to be managed to achieve a consistent product.

Composition and Specification

9. Results from five independent batches of cetylated fatty acids are reported by the applicant – see **Annex D** [Annex III COA's]. They suggest that the data demonstrate that the manufacturing process results in a consistent final ingredient that meets the specifications for the novel ingredient.

Table 2.c.1.1-1 Analytical Data for 5 Independent Representative Batches of Cetylated Fatty Acids (from p16 dossier)

Parameter	Method of Analysis	Specification Limit	Batch Number				
			1090l19/01	1090l19/02	1090l19/03	1090l19/04	1090l19/05
Physical status at 25°C	Visual	Solid	Pass	Pass	Pass	Pass	Pass
Colour (APHA colour)	AOCS Ea9-65	≤600	<600	<600	<600	<600	<600
Acid value (mg KOH/g)	AOCS Cd3d-63	≤5	0.8	0.7	0.7	0.4	0.8
Iodine value (g I_2/100)	AOCS Cd1-25	30 to 50	30.3	30.5	32.2	30.1	30.1
Saponification value (mg KOH/g)	AOCS Cd3-25	130 to 150	134.4	138.2	138.6	141.3	136.6
Hydroxyl value (mg KOH/g)	AOCS Cd13-60	≤20	6.3	7.1	6.0	4.1	7.4
Ester content (%)	GC-FID	70 to 80	75.14	74.38	74.23	72.19	73.49
Cetyl oleate (%)	GC-FID	22 to 30	23.95	23.80	23.77	23.10	23.48
Cetyl myristate (%)	GC-FID	41 to 56	49.37	48.82	48.69	47.39	48.25
Aluminium (mg/kg)	ICP-MS	≤2	1.57	1.26	1.03	1.49	1.70

APHA = American Public Health Association; AOCS = American Oil Chemists' Society; GC-FID = gas chromatography with flame ionisation detection; ICP-MS = inductively coupled plasma mass spectrometry; KOH = potassium hydroxide.

10. The applicant has analysed the fatty acid composition of the novel ingredient; the results are summarised in Table 2.c.1.2-1.

Table 2.c.1.2-1 Cetylated Fatty Acids Total Fatty Acid Composition (from p16 dossier)

Fatty Acid	Results
Oleic acid (%)	45.98
Myristic acid (%)	40.96
Linoleic acid (%)	7.97
Palmitic acid (%)	3.24
Stearic acid (%)	0.80
Palmitoleic acid (%)	0.44
Eicosenoic acid (%)	0.30
Lauric acid (%)	0.21
Eicosanoic acid (%)	0.11

11. The applicant has analysed triglycerides from the same five independent representative batches were determined using gas chromatography with flame ionisation detection (GC-FID); the results are summarised in Table 2.c.1.2-2.

Table 2.c.1.2-2 Triglyceride Analysis for 5 Independent Representative Batches of Cetylated Fatty Acids (from p17 dossier)

Parameter	Batch Number				
	1090l19/01	1090l19/02	1090l19/03	1090l19/04	1090l19/05
Total triglycerides (%)	22.83	23.81	24.82	24.85	22.84

12. The applicant has undertaken analysis of a number of undesirable substances. Information is provided on heavy metals, microbiology, glycidyl esters and 3-MCPD, dioxins and PCB's, PAH's and erucic acid. The applicant considers that the five independent batches analysed shows that the levels of undesirable substances are below legal limits and do not represent a safety concern.

Table 2.c.1.3.1-1 Heavy Metal Results for 3 Independent Representative Batches of Cetylated Fatty Acids (p17 dossier)

Parameter	EU Limit (in final food) as a Reference[a] (mg/kg wet-weight)	Batch Number			
		15F16411	19M19907	2007310-001	Method of Analysis
Arsenic (mg/kg)	0.3	<0.005	NT	<0.02	ICP-MS
Cadmium (mg/kg)	1.0	<0.005	0.008	<0.02	
Mercury (mg/kg)	0.1	<0.005	<0.005	<0.02	
Lead (mg/kg)	0.1	0.008	<0.005	<0.02	
Nickel (mg/kg)	NA	0.020	NT	NT	

EU = European Union; ICP-MS = inductively coupled plasma mass spectrometry; NA = not applicable; NT = not tested.
[a] Maximum levels according to Commission Regulation (EC) No. 1881/2006: for arsenic (rice waffles, rice wafers, rice crackers, and rice cakes), cadmium (food supplements), lead (fats and oils, including milk fat), and mercury (food supplements).

Table 2.c.1.3.2-1 Microbiological Analyses of 5 Independent Representative Batches of Cetylated Fatty Acids (p18 dossier)

Parameter	Method of Analysis	Specification	Batch Number				
			1090l19/01	1090l19/02	1090l19/03	1090l19/04	1090l19/05
Total aerobic microbial count (CFU/g)	ISO 4833	<10,000	<1,000	<100	<1,000	1,000	1,000
Escherichia coli (negative/g)	ISO 16649-2	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella (negative/25 g)	ISO 21528-1/2	Negative	Negative	Negative	Negative	Negative	Negative
Staphylococcus aureus (negative/g)	ISO 6888-1	Negative	Negative	Negative	Negative	Negative	Negative
Yeasts and Moulds (CFU/g)	ISO 21527-1/2	<100	<100	<10	<100	<100	<100
Enterobacter (CFU/g)	ISO 6579	<100	<100	<100	<100	<100	<100

CFU = colony-forming units; ISO = International Organization for Standardization.

Table 2.c.1.3.3-1 Results for 3-MCPD and Glycidyl Fatty Acid Esters in 5 Independent Representative Batches of Cetylated Fatty Acids (p19 dossier)

Parameter	EU Limit (in final food) as a Reference[a]	Batch Number				
		20E03517	1090l19/02	1090l19/03	1090l19/04	1090l19/05
3-MCPD and glycidyl fatty acid esters						
3-MCPD (µg/kg)	20	<10	-	-	-	-
Sum of 3-monochloropropanediol (3-MCPD) and 3-MCPD fatty acid esters, expressed as 3-MCPD (µg/kg)	1,250	-	210	230	260	240
Glycidyl fatty acid esters expressed as glycidol (µg/kg)	1,000	340	300	400	320	290

3-MCPD = 3-monochloropropanediol; EU = European Union.

[a] Maximum levels according to Commission Regulation (EC) No. 1881/2006 for 3-MCPD (hydrolysed vegetable protein); sum of 3-monochloropropanediol (3-MCPD) and 3-MCPD fatty acid esters, expressed as 3-MCPD (vegetable oils and fats, fish oils and oils from other marine organisms placed on the market for the final consumer or for use as an ingredient in food); and glycidyl fatty acid esters expressed as glycidol (vegetable oils and fats placed on the market for the final consumer or for use as an ingredient in food, with the exception of vegetable oils and fats destined for the production of baby food and processed cereal-based food for infants and young children).

Table 2.c.1.3.3-2 Results for Other Contaminants in an Independent Representative Batch of Cetylated Fatty Acids (p19 dossier)

Parameter	EU Limit as a Reference[a]	Batch 20E03517
Dioxins and PCBs		
Sum of dioxins (WHO-PCDD/F-TEQ) (pg/g fat)	0.75	0.098
Sum of dioxins and dioxin-like PCBS (WHO-PCDD/F-PCB-TEQ) (pg/g fat)	1.25	0.125
Sum of PCB28, PCB52, PCB101, PCB138, PCB153 and PCB180 (ng/g fat)	40	0.061
Polycyclic aromatic hydrocarbons		
Benzo(a)pyrene (µg/kg)	2	<0.5
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (µg/kg)	10	1.3
Erucic acid, including erucic acid bound in fat		
Erucic acid (g/kg)	20	<0.5

EU = European Union; PCB = polychlorinated biphenyl; WHO-PCDD/F-TEQ = the sum of the toxic equivalencies of the 17 most toxicologically significant dioxins and furans; WHO-PCDD/F-PCB-TEQ = total dioxin equivalency.
[a] Maximum levels according to Commission Regulation (EC) No. 1881/2006 for dioxins and PCBs (vegetable oils and fats), polycyclic aromatic hydrocarbons (oils and fats (excluding cocoa butter and coconut oil); and erucic acid, including erucic acid bound in fat (vegetable oils and fats placed on the market for the final consumer or for use as an ingredient in food, with the exception of camelina oil, mustard oil, and borage oil).

Specification

13. The applicant states that the specification parameters were assessed using internationally recognised methods or are otherwise determined using internally developed and validated methods.

Table 2.d-1 Proposed Specifications for Cetylated Fatty Acids (p26 dossier)

General Description		
Cetylated fatty acids is primarily composed of cetylated myristic acid and cetylated oleic acid.		
Parameter	**Specification**	**Method of Analysis**
Physical status at 25°C	Solid	Visual
Colour (APHA colour)	≤600	AOCS Ea9-65
Acid value (mg KOH/g)	≤5	AOCS Cd3d-63
Iodine value (g I_2/100)	30 to 50	AOCS Cd1-25
Saponification value (mg KOH/g)	130 to 150	AOCS Cd3-25
Hydroxyl value (mg KOH/g)	≤20	AOCS Cd13-60
Ester content (%)	70 to 80	GC-FID
Cetyl oleate (%)	22 to 30	GC-FID
Cetyl myristate (%)	41 to 56	GC-FID
Microbiological criteria		
Total aerobic microbial count (CFU/g)	≤1,000	ISO 4833-1:2013
Yeasts and moulds (CFU/g)	≤100	ISO 21527-1:2008

APHA = American Public Health Association; AOCS = American Oil Chemists' Society; CFU = colony forming units; GC-FID = gas chromatography with flame ionisation detection; HPLC = high-performance liquid chromatography; ICP/MS = inductively-coupled plasma mass spectroscopy; ISO = International Organization for Standardization; KOH = potassium hydroxide.

Stability

14. The stability of the novel ingredient was assessed using five independent batches of cetylated fatty acids. Data concerning physicochemical properties, biochemical properties and microbiological properties were reported – see **Annex D** [Annex IV stability].

15. The applicant suggests that the data from the real-time stability study at 25 +/- 2^{o}C demonstrates that cetylated fatty acids are stable for at least 18 months when stored under real-time conditions (p20 – 24 dossier).

16. The applicant suggests that the data from the accelerated stability study at 40 +/- 2^{o}C demonstrates that cetylated fatty acids are stable for at least 9 months when stored under accelerated conditions (p21 – 25 dossier).

History of Use

17. The applicant notes that while there is no history of use for the novel ingredient information on the history of use of the source materials is available. Information is provided on the olive oil. Highlighting Europe is one the largest producers, quoting figures from European Commission.

18. The applicant states that myristic acid and oleic acid are naturally occurring fatty aids. Oleic acid is found in high concentrations in olive oil and also pecan oil and peanut oil. Myristic acid is sourced from coconut oil, nutmeg butter, palm seed oil and milk fats.

19. Information is also provided on a similar product that has been authorised in Korea in 2009 with a different composition.

Proposed Use and Intake

20. Cetylated fatty acids are intended for use in food supplements for adults at 2.1 g/day and are not intended to replace any other food. Cetylated fatty acids are intended for use by adults in the general population; they are not intended for consumption by infants or young children.

21. The applicant has provided information on the combined intake of fatty acids from a range of sources in the diet. The applicant states that the intake level of 2.1 g/day of cetylated fatty acids is well below the maximum mean intake of 91 g/day for saturated fatty acids from a regular diet.

Absorption, Distribution, Metabolism and Excretion (ADME)

22. The applicant has not carried out ADME studies on cetylated fatty acids. Instead, the applicant states that the metabolism of fatty acids via the ß-oxidation pathway and the tricarboxylic acid cycle is well understood.

23. The applicant has also provided literature citations and a summary of the published in vivo ADME studies for oleic acid.

24. The applicant states that the metabolism of cetyl alcohol follows a similar metabolic pathway as fatty acids after absorption, firstly being oxidised to hexadecanal, which is rapidly oxidised to palmitic acid and in turn is metabolised *via* the fatty acid and tricarboxylic acid pathways.

Nutritional Information

25. The applicant states that the consumption of cetylated fatty acids would not be nutritionally disadvantageous for the consumer. This is based on the EFSA opinion concerning fatty acids as a food additive (EFSA ANS Panel, 2017). They explain that the novel ingredient is not intended to replace other sources of fatty acid. They also highlight that it contains Linoleic acid which is an essential fatty acid in the diet.

Table 2.h-1 Cetylated Fatty Acids Total Fatty Acid Composition (p35 dossier)

Fatty Acid	Results
Oleic acid (%)	45.98
Myristic acid (%)	40.96
Linoleic acid (%)	7.97
Palmitic acid (%)	3.24
Stearic acid (%)	0.80
Palmitoleic acid (%)	0.44
Eicosenoic acid (%)	0.30
Lauric acid (%)	0.21
Eicosanoic acid (%)	0.11

Toxicological Information

26. The applicant reports that results from a bacterial reverse mutation assay show that cetylated fatty acids are non-mutagenic at concentrations up to 5,000 µg/plate, in the absence or presence of metabolic activation (p39 dossier). The full study report is available in **Annex E**.

27. The applicant reports that results from an *in vitro* mammalian cell micronucleus test in human lymphocytes are non-clastogenic and non-

aneugenic in the absence and presence of metabolic activation, using a dose range which included the lowest precipitating dose level (p39 dossier). The full study report is available in **Annex E**.

28. A 14-day toxicity study has been undertaken, a dose of 4,500 mg/kg body weight/day was established as the no-observed-adverse-effect-level (NOAEL). This was considered to be a suitable high-dose for the subsequent 90-day study (p41 dossier). The full study report is available in **Annex E**.

29. The applicant reports a sub-chronic (90-day) oral toxicity study in rats utilising the OECD guide line 408 conducted to GLP principles. The novel ingredient was reported to be well tolerated at doses up to 4,500 mg/kg body weight/day (p43 dossier). The full study report is available in **Annex E**.

30. Information is also provided on data from the literature on the toxicology of the components of the novel ingredient to provide further evidence for the safety assessment.

Allergenicity

31. The applicant states that cetylated fatty acids are not expected to have any allergenic potential because the production process does not introduce any allergenic risks and none of the raw materials or processing aids contain any of the 14 allergens required to be labelled.

32. The applicant conducted analytical testing on the final ingredient for presence of several common allergens (casein, lactose, gluten and beta-lactoglobulin) and none of these were detected above the limit of detection.

Committee Action Required

● The Committee is asked whether the available data provide a satisfactory basis for evaluating the safety of this novel food ingredient.

● If so the Committee is asked whether it is content to recommend approval of the novel food as an ingredient to be added to the range of foods specified.

● If not, the Committee is asked to indicate what additional data would be required.

Annexes

ACNFP-150-03-Annex A – Request For Information

ACNFP-150-03-Annex B – Applicant's Response to Request For Information

ACNFP-150-03-Annex C – Dossier [Confidential]

ACNFP-150-03-Annex D – Annexes and Appendices [Confidential]

ACNFP-150-03-Annex E – Toxicology Study Reports [Confidential]

ACNFP-150-03-Annex F – References

ACNFP-150-03-Annex G – EFSA Opinion on NF