EVALUATION OF AUTOMATIC CLASS III DESIGNATION
FOR The Miris Human Milk Analyzer

DECISION SUMMARY

A. DEN Number:

DEN180007

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation of the Miris Human Milk Analyzer

C. Measurand:

Fat, carbohydrates, and proteins in breast milk

D. Type of Test:

Quantitative, mid-infrared spectroscopy

E. Applicant:

Miris AB

F. Proprietary and Established Names:

Miris Human Milk Analyzer (HMA)

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1493 Breast Milk Macronutrients Test System

2. Classification:

   Class II (Special Controls)

3. Product code(s):

   QEI

4. Panel:

   Clinical Chemistry (75)

H. Indications for Use:

1. Indications for Use:

   The Miris Human Milk Analyzer (HMA) quantitatively measures the concentration of fat, carbohydrate, and protein in human milk. The Miris HMA also provides calculated values for total solids and energy. These measurements, in conjunction with other clinical assessments, may be used to aid in the nutritional management of newborns, including preterm, and infants. This device is intended for use in healthcare by trained healthcare personnel at clinical laboratories.

2. Special conditions for use statement(s):

   For prescription use only.

   For central laboratory use. Not for point-of-care use.

   The Miris Human Milk Analyzer (HMA) is not the sole basis for nutritional management of the newborn. Use of the Miris HMA device is intended as part of an overall treatment plan and nutritional measures for newborns. The Miris HMA is an aid to the healthcare providers' standard of care assessment of nutritional management of newborns through monitoring of weight gain and growth.

   Do not use the HMA with fortified human milk or infant formula.

   Clinicians should follow clinical practice guidelines and standard of care when supplementing or fortifying human breast milk.

3. Special instrument requirements:

   Miris Human Milk Analyzer

I. Device Description:

The Miris Human Milk Analyzer (HMA) is a system for the quantitative measurement of fat, protein, and total carbohydrate content in human milk. The measurements of fat, protein and carbohydrate are also used in calculating the total solids and the energy content of human milk samples. The HMA unit includes a mid-infrared (mid-IR) spectroscopy system and a user interface. The user is guided by the interactive interface, via the screen, through the measurement process by use of the six-button controlled menu system. Milk samples (3 mL) are injected into the measuring unit (cuvette) via the instrument inlet using a syringe, with excess sample and waste exiting via the outlet.

The HMA device is comprised of a sample cuvette, hardware consisting of a mainboard and central processing unit (CPU) board, a display, touch button, fan, case, and consumables. The hardware consists of a mainboard with a CPU-board, detector board, and emitter board.

Consumables:

- Miris Check (provided) - This is a solution to be used during start up to check zero-level transmission.
- Miris Calibration Control Kit (provided)
- Miris Cleaner (provided)
- Syringes (provided)
- Distilled or deionized water (not provided)

J. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A3 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Third Edition, October 2014.

CLSI EP06-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline, April 2003.

CLSI EP07-A2 Interference Testing in Clinical Chemistry; Approved Guideline - Second edition, November 2005.

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - second edition, June 2012.

CLSI EP25-A Evaluation of Stability of In vitro Diagnostic Reagents; Approved Guideline, September 2009.

ISO 14971:2012 Medical devices - Application of Risk Management to Medical Devices, August 2012.

IEC 60601-1-2:2007 Medical Electrical Equipment - Part 1- 2: General Requirements for Basic Safety and Essential Performance - Collateral standard: Electromagnetic Compatibility - Requirements and Tests, March 2007.

EN/IEC 61010-1:2001 Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use - Part 1: General Requirements, February 2001.

K. Test Principle:

The Miris Human Milk Analyzer (HMA) detector contains four waveband filters, where three are used for detection of the macronutrients and one is a reference filter. The wavebands used for the macronutrients are specific for the functional carbonyl groups

(5.7μm) for fat determination, amide groups (6.5 μm) for protein determination, and hydroxyl groups (9.6 μm) for carbohydrate determination. The fourth waveband is a reference filter to correct, according Lambert-Beer's law, for variations in the optical path length in the liquid phase in the gap between the calcium fluoride windows. For determination of each component, the quantity of radiation absorbed by the functional groups is used, and estimations are made by reference to the amount of infrared radiation absorbed by water at the same waveband. The reference waveband is used to adjust for the background absorbance that is not derived from the presence of functional groups.

At a measurement, the HMA software application processes the transmission data via an internal calibration and presents values for fat, crude protein, true protein, and total carbohydrate concentrations (g/100 mL milk), and also calculated values for total solids (g/100 mL milk) and energy (kcal/100 mL milk), on the instrument display.

L. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility

The precision of the Miris Human Milk Analyzer was evaluated in accordance to the CLSI EP05-A3 guideline. A precision study was conducted at site 1, by testing a minimum of 3 milk samples using one device over 20 different days, with duplicate measurements per run and 2 runs per day for a total of 80 measurements per sample. Additional precision studies were conducted at sites 2 and 3, where milk samples were analyzed using one device over 5 days with triplicate measurements per run and 2 runs per day for a total of 30 measurements per sample. The results of the precision studies are summarized below:

Fat - Site 1

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	(b)(4)	(b) (4)				0.1302	17.6875	0.1374	18.6570
3						0.1443	7.6878	0.1450	7.7209
4						0.0433	1.3526	0.0609	1.9028
5*						0.0494	1.3409	0.0649	1.7636

*N=78, the number e 5 was unintentionally not tested in one run and no results were obtained.

Fat - Site 2

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.71	(b)(4)							
3	1.91								
4	(b)(4)								
5									

Fat - Site 3

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	(b)(4)								
3									
4									
5									

Crude Protein - Site 1

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
						SD	%CV	SD	%CV
3	0.80	(b) (4)				0.0433	5.3874	0.0542	6.7395
5*	(b) (4)					0.0160	1.5382	0.0501	4.8132
4	1.29					0.0274	2 .1148	0.0389	3.0038
1	2.77					0.2710	9.7807	0.2710	9.7807

*N=78, the number o 5 was unintentionally not tested in one run and no results were obtained.

Crude Protein - Site 2

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
3	(b)(4)								
5									
4									
1									

Crude Protein - Site 3

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
3	(b)(4)								
5									
4									
1									

True Protein - Site 1

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
3	(b)(4)								
5*									
4									
1									

*N=78, the number of results is reduced because sample 5 was unintentionally not tested in one run and no results were obtained.

True Protein - Site 2

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
3	(b)(4)								
5									
4									
1									

True Protein - Site 3

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
3	(b)(4)								
5									
4									
1									

Carbohydrates - Site 1

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
4	(b)(4)								
5*									
1									

*N=78, the number of results is reduced because sample 5 was unintentionally not tested in one run and no results were obtained.

Carbohydrates - Site 2

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
4	(b)(4)								
5									
1									

Carbohydrates - Site 3

Sample	Mean (g/100mL)	Between Day		Within Run		Between Run		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
4	(b)(4)								
5									
1									

b. *Linearity/assay reportable range:*

The linearity studies were conducted in accordance to CLSI EP06-A guideline. A minimum of 12 samples of known relative concentration (covering the range for the specific analyte) were prepared. The observed values were plotted against the expected values and linear regression analysis was performed. The results are provided in the table below.

Analyte	Concentration tested (g/100mL)	R^2	Slope	Intercept
Fat	0.4 – 4.8	0.9972	1.0119	-0.0724
Crude Protein	0.40 - 3.8	0.9964	0.9925	0.0364
True Protein	0.3 – 3.1	0.9967	0.9811	0.0647
Carbohydrates	6.1 - 8.9	0.9854	0.9457	0.5095

The results of the linearity study support the following claimed measuring ranges:

Analyte	Claimed range (g/100mL)
Fat	0.6 – 4.0
Crude Protein	0.8 – 3.0
True Protein	0.6 – 2.4
Carbohydrates	6.6 – 8.7

c. *Traceability, Stability, Expected Values (controls, calibrators, or methods):*

The Miris Human Milk Analyzer is traceable to certified reference materials and validated chemical methods. The validation of these chemical methods was reviewed and found to be acceptable. The applicant submitted a detailed traceability assurance plan which was reviewed and found to be acceptable.

Calibration stability:
A real-time calibration stability study was performed with five (5) Miris Human Milk Analyzers. A total of (b) (4) human milk samples were analyzed each day on each analyzer, [(b)(4)] days per week for up to [(b)(4)] weeks. The results demonstrate calibration is stable for up to [(b)(4)] weeks. The instrument should be re-calibrated by the manufacturer before the [(b)(4)]-week period if a transmission change of 10% or more for any filter is detected during the start-up process and after a major instrument servicing.

d. *Detection Limit:*

Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) of the Miris HMA was established using a 5-day study protocol per CLSI EP17-A2 guideline.

To evaluate the LoB, 3 replicate measurements were made on 4 blank samples per day across 5 days, on a single instrument for a total of 60 measurements. LoB was calculated using a non-parametric data analysis.

For the LoD and LoQ determination, 7 milk samples with low fat levels and 7 samples with low protein and carbohydrate levels were tested in triplicates across 5 days using 1 instrument and 1 operator. A total of 105 replicates per variable were obtained. LoD was calculated as LoD =LoB+ (b) (4) SD pooled, and LoQ was defined as the lowest amount of analyte that met a pre-determined total error (TE) of <30%. The results of LoB, LoD, and LoQ for each analyte are summarized below.

	Fat (g/100mL)	Crude protein (g/100mL)	True protein (g/100mL)	Carbohydrate (g/100 mL)
LoB	0.06	0.06	0.05	0.04
LoD	0.11	0.25	0.20	0.35
LoQ	0.41	0.42	0.34	3.00

e. Analytical Specificity:

Interference studies were conducted following the CLSI EP07-A2 guideline. The study was conducted by spiking 2 milk sample pools with two concentrations of each interferent substance. Each sample was analyzed on 2 devices during one analytical run, with 2 replicates per device. The difference between the test samples and control samples was calculated. The sponsor defined significant interference as a difference >0.10 g/100 mL for fat, crude protein, and true protein and >0.15 g/100mL for carbohydrates.

The compounds and the highest concentration that don't interfere are listed in the table below:

Interference	Maximum concentration tested that showed no interference (mg/L)
Acetaminophen	45
Ibuprofen	1.2
Aspirin	15
Oxycodone	0.60
Paroxetine	0.15
Gentamicin	0.6
Cefazolin	3
Diphenhydramine	0.3
Loratadine	0.90
Phenytoin	3
Carbamazepine	7.5
Hydrochlorothiazide	0.60
Propranolol	0.090
Metoprolol	0.450
Progestin only contraceptives	0.00075

Interference	Maximum concentration tested that showed no interference (mg/L)
(b)(4)	
Prednisolone	0.750
Domperidone	0.015
Morphine	0.150
Fluoxetine	0.300
Methyldopa	3
Caffeine	15
Bronopol	0.10%

The following substances were found to interfere and the sponsor states in the labeling that milk that may contain any of the drugs listed below should not be analyzed with the Miris HMA:

Interfering Substance	Concentration tested that caused interference (mg/dL)	Affected analytes
Citalopram	(b) (4)	Results in a negative bias on fat measurements
Sertraline		Results in a negative bias on fat measurements
Ampicillin		Results in a negative bias on fat measurements
Vancomycin		Results in a positive bias on fat measurements
Clindamycin		Results in a negative bias on fat measurements
Cephalexin		Results in a negative bias on fat measurements
Pseudoephedrine		Results in a negative bias on fat measurements
(b)(4)		Result in a positive bias on protein measurements.

The sponsor includes the following limitation in the labeling:
"Human milk may be contaminated with hemoglobin, from whole blood. This will result in a positive bias on protein measurements. If the milk is visibly pink, presumed from blood contamination, macronutrient analysis by HMA is not recommended."

f. *Assay Cut-off:*

Not applicable.

2. Comparison Studies:

a. Method Comparison with reference method:

The sponsor performed an accuracy study to determine the bias of the Miris Human Milk Analyzer (HMA) against validated comparative chemical methods. A total of 112 native human milk samples were tested in duplicate on 1 HMA device over 5 days. Regression analysis and bias estimations were based on first replicate results. The comparative method included the same 112 samples analyzed in triplicate. The mean of the triplicates results was used as the comparative values.

The results of the method comparison are summarized in the table below.

Analyte	N	Concentration tested (g/100mL)	R^2	Slope	Intercept
Fat	80	0.6 – 4.0	0.99	1.11	-0.11
Crude Protein	112	0.9–3.5	0.96	1.19	-0.33
True Protein	112	0.7– 2.8	0.96	1.19	-0.27
Carbohydrates	106	6.6 – 8.7	0.85	0.90	0.62
Total Solids*	112	9.8- 15.6	0.96	0.97	0.32

*calculated results from HMA compared to a validated chemical method.

The bias at low, medium, and high levels of each analyte was calculated. The results are presented in the table below.

Analyte	N	Range (g/100mL)	Concentration (g/100mL)	Bias (g/100mL)	95% CI
Fat	80	0.6- 4.0	(b) (4)		
Crude Protein	112	0.9- 3.5			
True Protein	112	0.7- 2.8			
Carbohydrates	106	6.6-8.7			

In addition, the sponsor conducted a method comparison study to evaluate the bias between the estimated energy values from Miris HMA method compared to a validated bomb calorimetric method. A total of (b)(4) native human milk samples were analyzed on the Miris HMA and the validated bomb calorimetric method. Data analysis and bias was estimated from the first replicate results obtained from the Miris HMA and triplicate means were used for the comparative method. The results of the regression analysis were:

(b) (4)

Bias of the energy results was estimated at three concentrations; the results are summarized below:

Energy (kcal/100mL)	Bias (kcal/100mL)	95% CI
45	(b) (4)	
70		
110		

b. Matrix comparison:

Not Applicable. The device is intended for use with human breast milk only.

3. Clinical Studies:

Not Applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

The composition of human milk is highly variable and affected by multiple factors such as diurnal variation, longitudinal changes associated with postpartum duration, time since last feed, volume of milk consumed at the prior feed, time during feed, and maternal physiological let down. The sponsor included in the labeling the breast milk composition variation in macronutrients in human milk which is based on meta-analysis results reported in the literature. The following tables are not intended to be used as expected values for milk supplementation.

Meta-analysis results of the macronutrient composition of term (37-42 weeks of gestation) human milk [1].

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1-3	1.8	0.7	2.0	0.6	2.0	0.9	5.6	0.6	1.6	0.2	54	8
Day 4-7	2.6	0.8	2.0	0.5	1.6	0.3	6.0	1.0	1.9	0.4	66	9
Week 2	3.0	0.9	1.8	0.4	1.3	0.2	6.2	0.6	1.9	0.4	66	9
Week 3-4	3.4	0.8	1.5	0.3	1.1	0.2	6.7	0.7	1.6	0.3	66	8
Week 5-6	3.6	1.1	1.1	0.2	1.0	0.1	6.1	1.0	1.4	0.3	63	7
Week 7-9	3.4	0.8	1.3	0.2	0.9	0.1	6.5	0.5	1.3	0.3	63	7
Week 10-12	3.4	0.9	1.2	0.2	1.0	0.1	6.7	0.7	-		63	8

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Colostrum (day1-3)	1.8				2.0		5.6				54	
Mature milk (week 5-12)	3.4				1.0		6.5				63	

Meta-analysis results of the macronutrient composition of preterm (<37 weeks of gestation) human milk [1]

Time After Delivery	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Lactose (g/100mL)		Oligo-saccharides (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1-3	2.2	0.9	2.8	1.1	2.7	1.5	5.1	0.7	-		49	7
Day 4-7	3.0	1.2	2.1	0.5	1.7	0.5	6.3	1.1	2.1	0.4	71	9
Week 2	3.5	1.1	1.9	0.4	1.5	0.4	5.7	0.8	2.1	0.5	71	12
Week 3-4	3.5	1.0	1.6	0.4	1.4	0.4	6.0	0.5	1.7	0.3	77	8
Week 5-6	3.2	0.8	1.4	0.3	1.1	0.2	5.8	0.6	-		70	5
Week 7-9	3.3	0.9	1.1	0.2	1.1	0.2	6.3	0.4	-		76	8
Week 10-12	3.4	1.5	1.3	0.3	1.0	0.2	6.8	0.3	-		-	
Colostrum (day1-3)	2.2				2.7		5.1				49	
Mature milk (week 5-12)	3.3				1.1		6.2				73	

Macronutrient composition of donor human milk.

Reference	Fat (g/100 mL)		Crude Protein (g/100 mL)		True Protein (g/100mL)		Carbohydrate (g/100mL)		Energy (kcal/100mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	M	SD
[2]	3.2	1.0	1.2	0.5	-		7.7	0.9	65	9
[3]	3.6		0.9		-		7.2		67	

References:

[1] D. Gidrewicz and T. Fenton. "A systematic review and meta-analysis of the nutrient content of preterm and term breast milk", BMC Pediatrics 14:216, 2014.

[2] K. Wojcik, D. Rechtman, M. Lee, A. Montoya, and E. Medo. "Macronutrient analysis of a nationwide sample of donor breast milk". JAm Diet Assoc, vol. 109, pp. 137-140, 2009.

[3] K. Michaelsen, L. Skafte, J. Badsberg, and M. Jorgensen. "Variation in macronutrients in human bank milk: Influencing factors and implications for milk banking". Journal of Pediatric Gastroenterology and Nutrition, vol. 11, pp. 229-239, 1990.

M. Instrument Name

Miris Human Milk Analyzer

N. System Descriptions:

1. Modes of Operation:
   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device? Yes __X__ or No _____
   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission: Yes ___or No __X__.

2. Software:
   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes __X__ or No _____

3. Specimen Identification:
   Samples are given a unique identifier.

4. Specimen Sampling and Handling:

   Human milk, in liquid form, is the only type of sample that should be used in this assay. Thawed milk can be kept at room temperature (20-30°C) for a maximum of 2 hours or refrigerated for max 48 h (unpreserved)/max 72 h (preserved). Frozen samples maximum recommended storage duration is 6 months (unpreserved) and up to 12 months (preserved). Recommendations are provided in the labeling for sample handling and processing for storage

5. Calibration:

   The instrument is calibrated at the manufacturer site. Standard operating procedures are followed and performed on up to (b)(4) instruments per calibration batch. Calibration is performed using (b)(4) calibration samples designed to cover the instrument calibration range of each analyte (fat, protein, carbohydrates). The calibration samples are prepared, and values are assigned using validated methods.

6. Quality Control:

The sponsor recommends running quality control (QC) materials prior to analyzing patient samples to ensure the Miris Human Milk Analyzer is working as intended. Laboratories should follow federal, state, and local guidelines for testing QC.

O. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Carryover:
Studies were performed to determine if the level of carryover for the assay is acceptable. Samples with high and low concentrations of the analytes were injected in a predetermined order and percent of carryover was calculated. Specific carry-over was (b)(4) for water to milk carry-over (b)(4) and (b)(4) for milk to water carry-over (b)(4)

Electrical Safety and Electromagnetic Compatibility (EMC):

Electrical safety and EMC testing were conducted on the Miris Milk Analyzer. The system complies with IEC 60601-1-2, IEC 61010-2 standards for safety and IEC 61326-1 for EMC.

P. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

Q. Identified Risks and Required Mitigations:

Identified Risks to Health	Required Mitigations
Incorrect test results	General controls and special controls (1) and (2)
Incorrect action based on test results	General controls and special control (2)

R. Benefit/Risk Analysis:

Summary of the Assessment of Benefit
For the Proposed Indications for Use
The Miris Milk Analyzer (HMA) quantitatively measures the concentration of fat, carbohydrate, and protein in human milk. The instrument also provides calculated values for total solids and energy. These measurements may be used to aid in the nutritional management of neonates and young infants at risk for growth failure due to prematurity or other medical conditions. This device will be helpful in management of post-natal growth failure in neonates and young infants with medical conditions, including premature birth. These patients may benefit from human milk fortification to achieve macronutrient content to support optimal growth. A reasonable probability of benefit is expected since there are no other ways to measure these macronutrients in the clinical laboratory and the current practice

of managing these infants relies on assumed macronutrient content of human milk, along with clinical measurements and the judgment of the treating physician. If available human milk is found to be sub-optimal for the nutritional needs of the infant, targeted fortification of the breast milk can be undertaken. Such fortification will not be determined in isolation but will be pursued in conjunction with the clinical status of the infant, serial growth measurements, and the clinical judgment of the treating physician. The benefits of this device may be of both a short-term or long-term nature. In the short term, the infant's nutritional status may improve, leading to improved growth patterns based on assessments of weight, length, and head circumference. Improved growth and overall health status in the neonatal period and infancy are linked to long-term improvements in growth and development.

Summary of the Assessment of Risk

For the Proposed Indications for Use

The risk of falsely elevated results is an overestimation of macronutrients which could lead to under-fortification of the milk given to the neonate or infant, and which, over a long period of time, may result in suboptimal growth and development.

The risk of a falsely low result is an underestimation of macronutrients, which, over a long period of time, could lead to over-fortification of the milk given to the neonate or infant, with potential risk of feeding intolerance, neonatal necrotizing enterocolitis (NEC), or other complications.

The use of the HMA device is intended as part of an overall treatment plan and other nutritional measures for newborns. HMA is not intended to be used in isolation; rather, it is an aid to the healthcare providers' standard of care assessment of nutritional management of newborns/infants through monitoring of weight gain and growth patterns.

Summary of the Assessment of Benefit-Risk

For the Proposed Indications for Use

Given that there are possible risks associated with an incorrect test result and the incorrect clinical actions based on the test results, the benefit-risk balance of this device is undetermined and requires additional mitigations in the form of limitations and special controls, beyond general controls.

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies

For the Proposed Indications for Use

Overall, the possible benefits of the Miris HMA in aiding the nutritional management of infants outweigh the likelihood of suboptimal growth, the development of feeding intolerance, or other complications which may develop as a result of possible errors, when considering the mitigations provided by the limitations and special controls, beyond general controls. The labeling also states that assay results should be used only as an aid in the nutritional management of infants and not as the sole basis for making nutrition decisions, which mitigates the risk of over-reliance on the device.

Design verification and validation activities regarding performance characteristics conducted showing acceptable results and labeling regarding limitations of the device are mitigations to the risk of over reliance on the test and erroneous results.

No device for the quantitative measurement of fat, carbohydrate, protein, total solids, and energy in human milk, to determine the nutritional management needed to optimally supplement human milk for prematurely born neonates and infants, is currently cleared or approved in the U.S. Chemical reference methods for protein, fat, and carbohydrates may be used in research laboratories but are not widely available for clinical application. Such methods require large quantities of the breast milk (20 mL) for analyses and three days to get the results due to the labor-intensive nature of these procedures. The Miris HMA only requires 3 mL of breast milk for a complete measurement of the macronutrients and results are given within one minute.

The device is highly desired by treating doctors and medical staff and among parents as an aid in nutritional management of neonates and young infants, including those born preterm or with special nutrient requirements.

Treating doctors and other medical staff will be able to better guide their decisions on when to fortify human milk based on the individual need for each patient. This is particularly important for premature or very low birthweight infants, to optimize nutritional intake to promote normal growth and development. The major risk is that the device over- or underestimates the protein or energy concentration in the milk over a significant period of time. Undernutrition over a prolonged time can lead to growth failure and suboptimal development for neonates or young infants born preterm or with health conditions that require increased energy provision. Overnutrition over a prolonged period may also lead to complications for the neonate and young infant. There is a risk relating to unknown performance of this device outside of the intended use population. Risks relating to utilization outside of the intended use population are mitigated by appropriate labeling and indication for prescription use only. Similarly, over-reliance on device results should be mitigated by appropriate labeling and requirement for prescription use (indicating the test results are an aid to be used in conjunction with clinical factors and not to be relied upon as a sole determinant of nutritional management). No treatment advice or recommendations to treat any newborn are provided based on the results of the HMA analysis. Rather, the device is an aid in assessing macronutrient levels in breast milk, so that the healthcare provider may use this information in conjunction with clinical assessments, to make decisions about nutritional management.

Overall, the test's performance characteristics have been characterized and are suitable for the intended use of the device as an aid in nutritional management. Given the device's indications for use, required general controls, and special controls established for this device (e.g., labeling and studies performed), the probable benefits outweigh the probable risks, and granting de novo classification of this device into Class II is appropriate.

S. Conclusion:

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 862.1493. FDA believes that the stated special controls, and applicable general controls including design controls, provide reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code:	QEI
Device Type:	Breast milk macronutrients test system
Class:	II (special controls)
Regulation:	21 CFR 862.1493

(a) Identification.

A breast milk macronutrient test system is a device intended to quantitatively measure fat, protein, and total carbohydrate content in human breast milk. These measurements, in conjunction with other clinical assessments, may be used to aid in the nutritional management of infants.

(b) Classification. Class II (special controls). A breast milk macronutrient test system must comply with the following special controls:

(1) Design verification and validation must include the following:
- (i) An appropriate traceability plan, as determined by FDA, to minimize the risk of drift in the breast milk macronutrient test system results over time.
- (ii) Data that demonstrate appropriate precision, as determined by FDA, of the breast milk macronutrients test system. Precision studies must include assessment of a minimum of three breast milk specimens containing different concentrations (low, medium and high levels) of fat, carbohydrates, and protein. Precision data must include breast milk specimen measurements that are collected at a minimum of three laboratory sites.
- (iii) Data that demonstrate appropriate measurement accuracy, as determined by FDA, of fat, carbohydrates, and protein in breast milk. Measurement accuracy data must include breast milk specimen measurements that are collected at a minimum of one laboratory site.
- (iv) Data from studies appropriate, as determined by FDA, to demonstrate that the device is free from significant interference from substances that could be present in human milk, including hemoglobin, and medications that are used by breastfeeding subjects.

(2) The 21 CFR 809.10 labeling must include the following:
- (i) A limiting statement indicating that the results should be used only as an aid in the nutritional management of infants and not as the sole basis for making nutrition decisions.