EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
OMNIgene•GUT Dx
DECISION SUMMARY

A. DEN Number:

DEN200040

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the OMNIgene•GUT Dx

C. Measurands:

Storage and stability of bacterial DNA from human fecal specimens.

D. Type of Device:

Device to preserve and stabilize relative abundances of microbial nucleic acids in clinical samples

E. Applicant:

DNA Genotek Inc.

F. Proprietary and Established Names:

OMNIgene•GUT Dx

OMD-200

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.2952

2. Classification:

   Class II

3. Product code(s):

   QPO

4. Panel:

   83- Microbiology

H. Indications for Use:

1. Indications for use:

   OMNIgene•GUT Dx is intended for the non-invasive collection of human fecal samples and the stabilization of DNA from the bacterial community for subsequent assessment of the microbiome profile by an assay validated for use with OMNIgene•GUT Dx.

2. Special conditions for use statement(s):

   For *in vitro* diagnostic use only
   For prescription use only

3. Special instrument requirements:

   None

I. Device Description:

The OMNIgene•GUT Dx device consists of a collection tube with a tube top and pusher cap with a screw seal, along with a spatula or spoon for transferring fecal specimen into the collection tube. The tube contains 2 mL of the stabilizing liquid and a stainless-steel mixing ball. These components are intended to stabilize bacterial DNA in human fecal specimens, notably to preserve the relative abundances of bacterial organisms, for potential downstream analysis of the fecal microbiome. The collection device is designed for storage of fecal specimens at room temperature (20-26°C/68-79°F) for up to 30 days.

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

Not applicable

K. Test Principle:

Not applicable

L. Performance Characteristics:

1. Analytical performance:

   a. *Whole Genome Sequencing (WGS) Assay Validation*

   To assess collection device performance, a whole genome sequencing assay workflow was validated. This validation included defining a microbiome panel of [redacted] bacterial species and quantitating the Limit of Blank, Limit of Detection, Lower Limit of Quantitation, Upper Limit of Quantitation, Lower Baseline Read Count Limit, Upper Baseline Read Count Limit, and Range (see definitions below) for each of these [redacted] bacterial species in the microbiome panel (MP). Using these established limits and ranges for this panel, the device performance was quantitated in terms of stabilization of bacterial DNA as well as specifically the preservation of relative abundances of these specific bacterial members within fecal specimens, described as "neutrality".

   Definitions of Terms:
   Background DNA Mixture (BDM) – Since WGS enumerates all DNA molecules present in a library preparation, the ability to detect targets of interest is directly proportional to the abundance of the target and the presence of other non-target or 'background' DNA molecules. A mixture of non-target DNA (bacterial in origin) has been created to serve as a diluent, for the determination of LoD, LoQ and Range for targets in the Microbiome Panel.
   Limit of Blank (LoB) – The highest measurement result that is likely to be observed for a blank sample.
   Limit of Detection (LoD) - The Lowest amount of analyte in a sample that can be detected above the defined Limit of Blank.
   Lower Limit of Quantitation (LLoQ) - The lowest amount of analyte in a sample that can be quantitatively determined with acceptable precision and trueness.
   Upper Limit of Quantitation (ULOQ) - The highest amount of analyte in a sample that can be quantitatively determined with acceptable precision and trueness.
   Range - Dynamic range for reliable quantification of WGS reads will be established through contrived sample sequencing and analysis. This per species range falls between the ULOQ and LoD determined in the assay validation for each species and will be applied across all sequencing studies.
   Lower Baseline Read Count Limit (l-BRCL) – The minimum read count a species can have within a baseline sample (e.g. an unstabilized (fresh) sample for neutrality tests; a T0 sample for stability tests) in order for the pair of samples from a donor to be included in testing for that species. l-BRCL is a species-specific value, which will be calculated for each species during assay validation, based on the LLoQ for that species.
   Upper Baseline Read Count Limit (u-BRCL) – The maximum read count a species can have within a baseline sample (e.g. an unstabilized (fresh) sample for neutrality tests; a T0 sample for stability tests) in order for the pair of samples from a donor to be included in testing for that species. u-BRCL is a species-specific value, which will

be calculated for each species during assay validation, based on the ULOQ for that species.

Microbiome Panel Members

Species ID	Family
(b)(4)	

The members of this panel were selected based on the following criteria:

- High prevalence (b)(4) in representative donor population
- Abundance (b)(4) in donors where species is present
- Representative species from major bacterial families on the gut microbial community phylogenetic tree: (b)(4) (b)(4)
- Gram-negative and Gram-positive bacteria are represented
- Genomes range in GC content from (b)(4)

Additionally, a pathogenic species from the (b)(4) family was included in the panel as well as three pediatric relevant species.

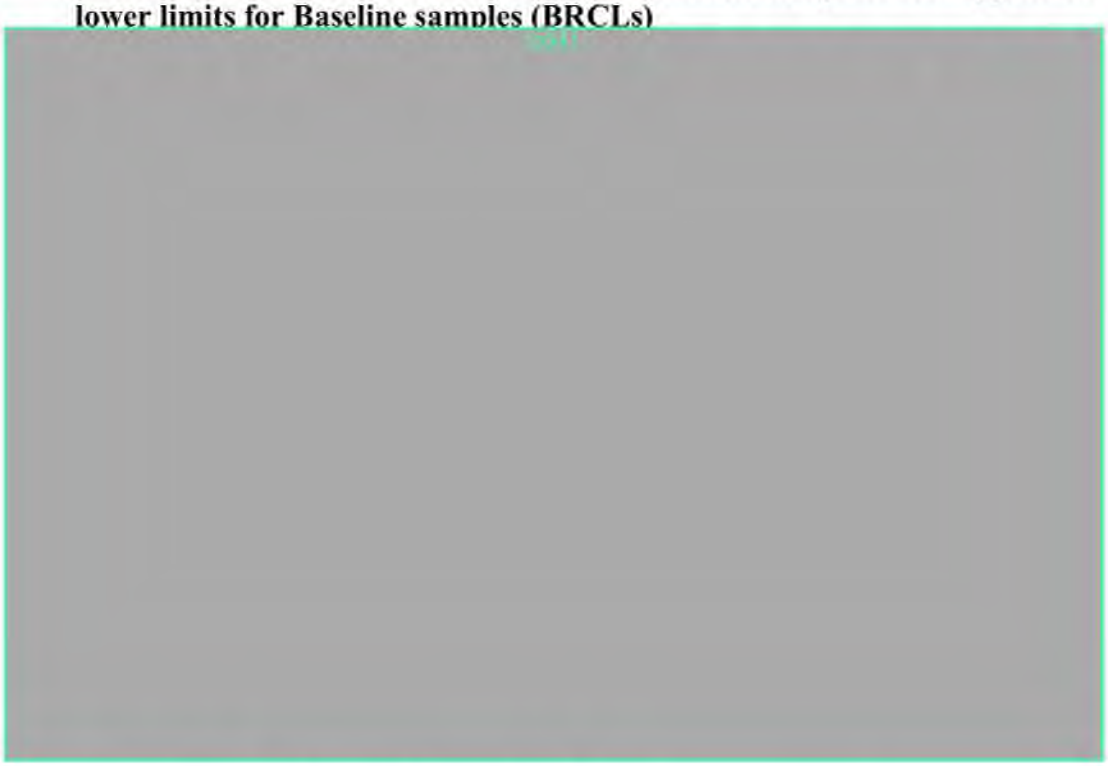
Lower and Upper Baseline Read Count Limits:

The purpose of the lower and upper Baseline Read Count Limits (l-BRCL and u-BRCL) was to define a read count range for baseline samples that was contained within the overall quantifiable range of the WGS assay. This was done to ensure that if the read counts of a microbiome panel species changed over time or in response to an external challenge, the change from baseline was quantifiable and did not immediately exceed the lower and upper quantification limits.

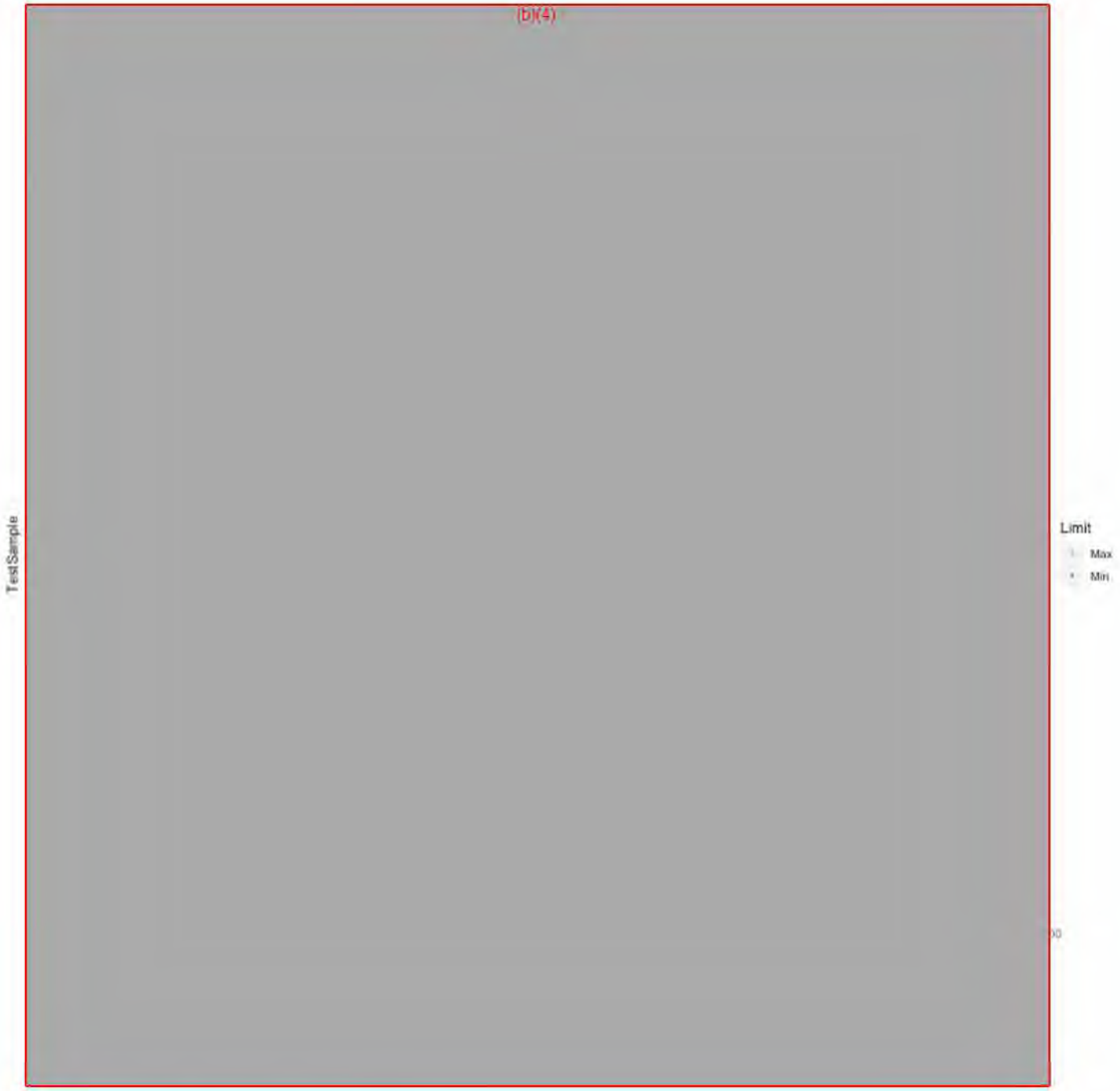
The LoQ values (LLoQ and ULoQ) were used to calculate the lower and upper Baseline Read Count Limit (l-BRCL and u-BRCL). The calculated upper and lower BRCL for each species was used in the screening of donors for OMNIgene•GUT Dx sample collections.

The per-panel species defined Limits and Ranges are summarized below.

Summary of Final Limits and Range for the WGS assay and the upper and lower limits for Baseline samples (BRCLs)



Test Sample Read Count Limits (TeSaRCol):
The above defined WGS assay limits are designed to define the read count range in which a Microbiome Panel species can be tested with confidence. The OMNIgene·GUT Dx analytical testing used these limits in the context of the Test Sample Read Count Limit (TeSaRCol) method (Figure 1).



b. Stability and Neutrality Studies

This section describes two studies evaluating device performance in terms of:

1. Microbiome Relative Abundance Preservation ("Neutrality")
2. Room Temperature Storage Stability

These studies were conducted in two population cohorts, which followed identical study designs:

- Adult Cohort – 30 minimum donors, ages 18+ years
- Pediatric Cohort – 30 minimum donors, ages 3-46 months

Fecal collection occurred at either the donor's home or a collection site following provided user instructions. For the pediatric cohort, the actual collection was performed by a parent/guardian. Specimens were collected under an institutional review board (IRB) approved protocol and informed consent was obtained prior to collection. Collection was performed using a container (not the candidate device) without the stabilization liquid to a fill-to line to acquire bulk specimen, which was sent to the processing lab on ice within 24 hours of collection (adult cohort) or 48 hours of collection (pediatric cohort).

Donor Screening and Inclusion:
A sample from each donor was screened to ensure that each donor met set inclusion criteria for these studies. For adult donors to be included, screened fecal specimens had to contain a minimum of 10 species from the Microbiome Panel ((b)(4)) within Baseline Read Count Limits determined during the WGS assay validation study. Additionally, each adult relevant species of the Microbiome Panel ((b)(4)) had to be represented in the screened sample within BRCLs by a minimum of ((b)(4)) donors. The clinically relevant species in the Microbiome Panel ((b)(4)) was evaluated as it appeared and had no criteria for minimum number of donors.

For pediatric donors to be included, due to inherent low prevalence and lack of species diversity in the youngest pediatric donors, each pediatric sub-cohort had different inclusion criteria, which increased with age to reflect the change to an adult-like microbial diversity. Specifically, the screened sample from the pediatric donor must have the minimum number of species (listed below) from the Microbiome Panel within their BRCLs as determined during assay validation:

- 3-14 months: Minimum of 2 species total, with a minimum of 1 species from ((b)(4)) specifically
- 15-30 months: Minimum of 6 species total, no restrictions on which species
- 31-46 months: Minimum of 8 species total, no restrictions on which species

Each pediatric relevant species of the Microbiome Panel ((b)(4)) must be represented in the screened sample within BRCLs by a minimum of 10 donors.

Study Procedures:

((b)(4))

(b)(4)

Control samples included 1 *positive specimen control (PSC)* (b)(4)

(b)(4)

(b)(4) One (1) *negative specimen control (NSC)* sample was included (b)(4)

(b)(4)

(b)(4) . One (1) *no template control (NTC)* was included (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) . Normalized libraries were pooled together (b)(4)

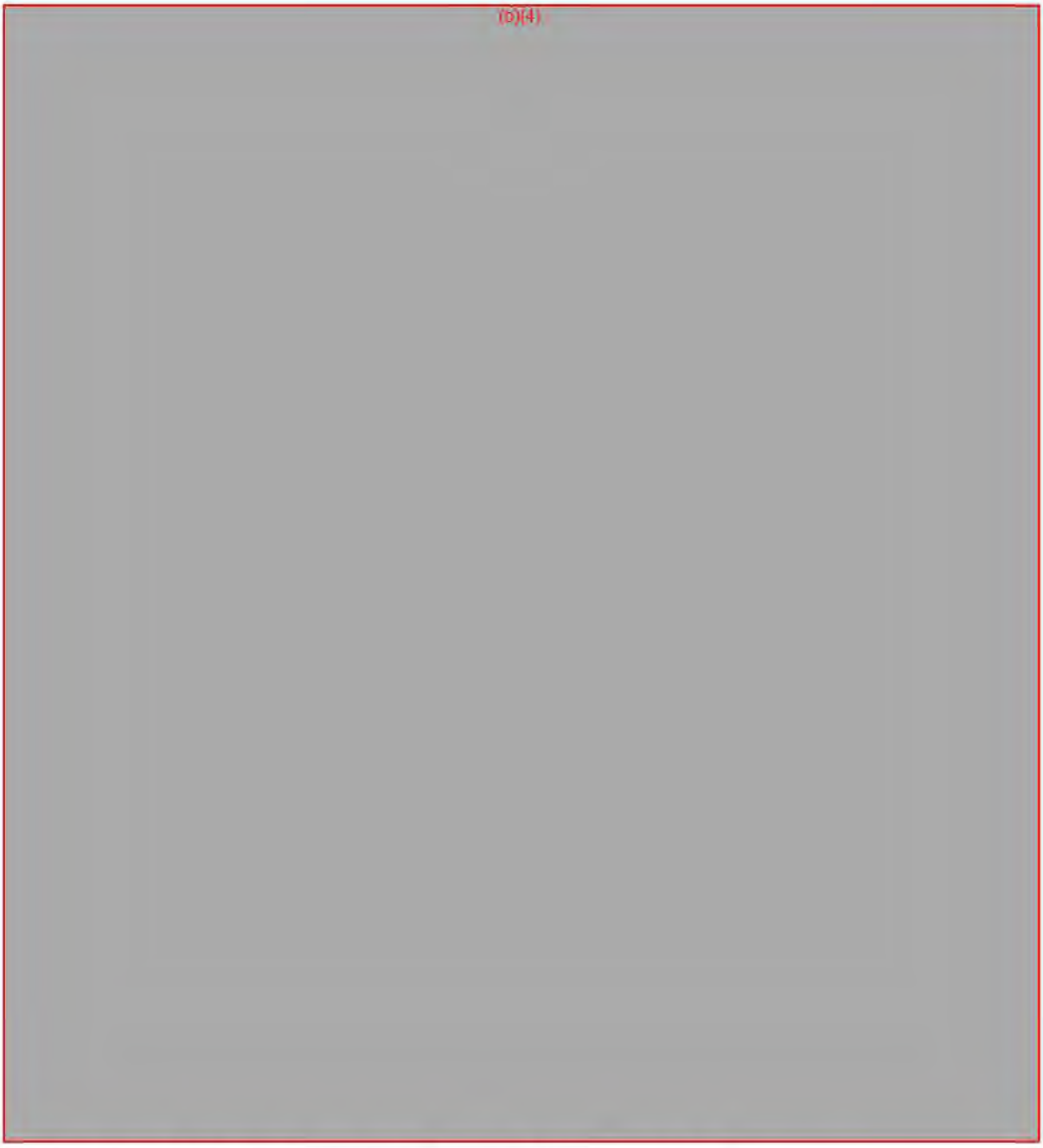
(b)(4)

(b)(4) loaded onto the cartridge and the sequencing run is started. Sequencing

was done on the Illumina NextSeq 550 (b)(4) (b)(4). Note that each step (extraction, quantification, library prep, sequencing) was individually validated using the same principles as described above for the whole genome sequencing assay.

WGS Bioinformatics Analysis Procedure:

(b)(4)



Microbiome Relative Abundance Preservation ("Neutrality"):

The objective of this "Neutrality" study was to validate the ability of the OMD-200 device to not interfere with the microbial community composition at the point of collection such that it maintains an unbiased representation of the *in vivo* state, i.e. preserves the relative abundances of bacterial organisms in the specimen. This study compared fecal specimens collected in OMD-200 devices containing the stabilization liquid ("OMD-200 baseline") to fecal specimens from the same donor collected without the stabilization liquid contained within the OMNIgene·GUT Dx device ("unstabilized control baseline").

While this study initially included 45 donors, only 30 total donors were included in the final dataset after screening donors for specified inclusion criteria identified in the

donor screening section above. Importantly, the OMD-200 baseline specimen data from this study were also used for the room temperature storage stability study described below.

Number of Donor Specimens and Extracted Samples in Neutrality Study

	Number of Donors	**45**
Control Specimens without Stabilization Liquid	# specimens collected per donor	1
	# of DNA extractions per specimen	1
	Total # extracted control specimens	45
	Total # of control specimens in final dataset	30
OMD-200 Collected Specimens	# specimens collected per donor	1
	# of DNA extractions per specimen (OMD Baseline)	1
	Total # extracted OMD-200 specimens	45
	Total # extracted OMD-200 specimens in final dataset	30
	Total # of Extracted Samples	**90**
	Total # of Samples for Final Data Set	**60**

Representation of Microbiome Panel species in the adult cohort of the neutrality study

Species ID	Total Number of Donors

Representation of Microbiome Panel species in the pediatric cohort of the neutrality study

Species ID	Total Number of Donors

Species ID	Total Number of Donors
[redacted]	

Pediatric Sub cohort representation in the neutrality study

Pediatric Sub-Cohort	# Donors	Representation
3-14 months	10	33.3%
15-30 months	12	40.0%
31-46 months	8	26.7%

Microbial community consistency between control and test samples was evaluated based on whether rarefied species-level read counts for each Microbiome Panel species in the test samples fell within TeSaRCol range calculated from the unstabilized control sample:

[redacted]

Neutrality Acceptance Criteria:

The acceptance criteria for this study included a total DNA yield ≥ 120 ng [redacted] per extraction aliquot in ≥ 95% of samples. Additionally, microbial community neutrality is demonstrated as follows:

- Per donor, each Microbiome Panel species in the stored sample has read counts within the TeSaRCol range as calculated above using the unstabilized Control Baseline
- Neutrality per Microbiome Panel species will be demonstrated in ≥ 90% of donors that were successfully screened to contain that species

Neutrality Results:

For the neutrality study, microbial DNA [redacted]

(b)(4)

(b)(4) The results of this study showed that all species examined as part of the Microbiome Panel demonstrated neutrality in ≥ 90% of donors between unstabilized and OMD-200 fecal samples. Furthermore, for both the adult and pediatric cohorts evaluated, 100% of specimens met the DNA yield acceptance criteria of 120 ng (b)(4).

Statistical summary of OMD-200 device DNA yields (µg) for neutrality samples of both cohorts

		Adult Cohort	Pediatric Cohort
(b)(4)	(b)(4)		
	Mean ± SD	11.98 ± 4.37	9.69 ± 5.65
	95% CI of Mean	10.35, 13.62	7.58, 11.81
	Median	11.45	8.51
	Min, Max	5.10, 26.47	2.41, 27.81
	% ≥ (b)(4)	100%	100%

Room Temperature Storage Stability:

The objectives of this stability study were to validate the ability of the OMD-200 device to stabilize the microbial community composition during room temperature storage and to validate that the addition of the OM-LQR processing reagent does not impact the ability of the OMD-200 device to stabilize samples during room temperature storage (20°C - 26°C).

Number of Donor Specimens and Extracted Samples in Room Temperature Stability Study

	Number of Donors	(b)(4)
RT Storage With OM-LQR	# specimens collected per donor	
	# of DNA extractions per specimen	
	Total # extracted specimens	
RT Storage Without OM-LQR	# specimens collected per donor	
	# of DNA extractions per specimen	
	Total # extracted specimens	
Total # of Extracted Samples		
Total # of Samples for Final Data Set		

(b)(4)

*30 samples are the shared OMD Baseline samples extracted as part of neutrality testing.

Representation of Microbiome Panel species in the adult cohort of room temperature stability study

Species ID	Total Number of Donors
(b)(4)	

Pediatric Sub cohort representation in the room temperature storage study

Pediatric Sub-Cohort	# Donors	Representation
3-14 months	8	26.7%
15-30 months	17	56.7%
31-46 months	5	16.7%

Representation of Microbiome Panel species in the pediatric cohort of room temperature storage stability study

Species ID	Total Number of Donors
(b)(4)	

(b)(4)

(b)(4)

Room Temperature Storage Stability Acceptance Criteria:
The acceptance criteria for this study included a total DNA yield ≥ 120 ng ((b)(4) per extraction aliquot in ≥ 95% of samples. Additionally, microbial community stability is demonstrated as follows:

- Per donor, each Microbiome Panel species in the stored sample has read counts within the TeSaRCol range as calculated using the OMD Baseline
- Stability per Microbiome Panel species will be demonstrated in ≥ 90% of donors that were screened to contain that species

Room Temperature Storage Stability Results:
For both the adult and pediatric cohorts evaluated, 100% of specimens met the DNA yield acceptance criteria of 120 ng ((b)(4) . Furthermore, all species examined as part of the Microbiome Panel demonstrated stability in ≥ 90% of donors when stored at room temperature for up to 30 days either with or without the addition of OM-LQR (auxiliary liquefaction reagent).

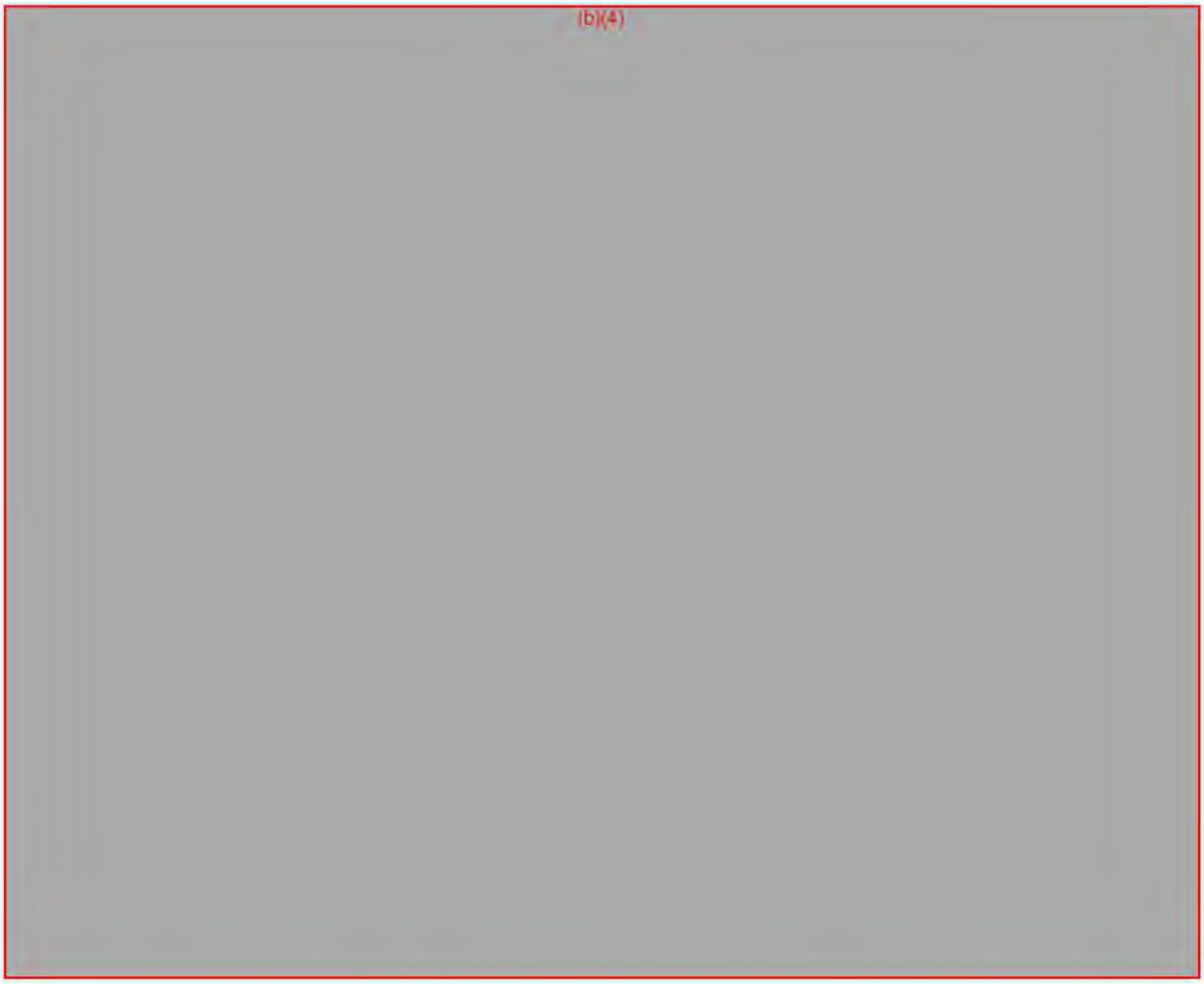
Statistical summary of DNA yields (µg) for room temperature stability samples of both cohorts.

	Adult Cohort	Pediatric Cohort
(b)(4)		

c. *Reproducibility Study*

The primary objectives of this study were to evaluate: 1) performance reproducibility of the OMD-200 collection device across multiple device lots when used to collect from the same fecal sample, and 2) microbiome profile reproducibility across multiple aliquots of the same OMD-200 collected fecal sample. (b)(4)

(b)(4)



Three different lots of OMD-200 devices, each containing a different lot of stabilizing solution, were used. The same sample was collected into one device from each lot to evaluate the reproducibility between device lots. To evaluate the reproducibility between aliquots, five aliquots were sequentially taken from the same collected OMD-200 sample. This study included 14 donors in the final dataset. These 14 were selected after screening for the inclusion criteria (b)(4) (b)(4) section of the adult cohort.

Number of Donor Specimens and Extracted Samples in the Lot-to-lot Reproducibility Study

Total Number of Donors	14
Number of specimens collected per donor	3
Number of specimens collected per lot	14
Number of DNA extractions per specimen	1
Total # of Extracted Samples for Final Data Set	**42**

Number of Donor Specimens and Extracted Samples in the Aliquot-to-aliquot Reproducibility Study

Total Number of Donors	14
Number of specimens collected per donor	1
Number of DNA extractions per specimen	5*
Total # of Extracted Samples	**56**
Total # of Samples for Final Data Set	**70***

*One extraction was performed during the Lot-to-lot Reproducibility Study

Reproducibility Study Procedures:
From a single specimen, each donor collected (b)(4) aliquots into (b)(4) OMD-200 devices, representing (b)(4) unique device lots. Specimens were received and processed by lab personnel. (b)(4) (b)(4) (b)(4) All aliquots from one donor were extracted by a single operator. DNA was extracted, quantified, sequenced, and analyzed. Consistency in microbial community composition across samples was assessed based on the coefficient of variation (CV) of classified read counts post-rarefaction.

Representation of Microbiome Panel species in the donor cohort

Species ID	Number of donors

Reproducibility Acceptance Criteria:
The acceptance criteria for this study included a total DNA yield ≥ 120 ng (0.12 µg) per extraction aliquot in ≥ 95% of samples. Additionally, microbial community composition consistency is shown as follows:

- CV of classified read counts post-rarefaction ≤ 30% for each Microbiome Panel Species between all (b)(4) samples per donor (lot-to-lot assessment) or between all (b)(4) aliquots per donor (aliquot-to-aliquot assessment).
- Consistency is demonstrated in ≥ 90% of donors per Microbiome Panel species

Reproducibility Results:
All specimens for reproducibility assessment both lot-to-lot and aliquot-to-aliquot met the DNA yield acceptance criteria of 120 ng (0.12 µg). Furthermore, consistency of the microbial composition was demonstrated by a CV ≤ 30% for each Microbiome Panel Species of all donors investigated as part of both the lot-to-lot and aliquot-to-aliquot assessments

Statistical summary of DNA yields (µg) from samples used to assess lot-to-lot reproducibility

		Lot A	Lot B	Lot C	Overall
Total DNA Yield (µg/aliquot) Acceptable Minimum = 0.12 µg	**N**	14	14	14	42
	Mean ± SD	8.06 ± 4.97	7.56 ± 4.66	7.50 ± 5.15	7.71 ± 4.81
	95% CI of Mean	5.19, 10.93	4.87, 10.25	4.53, 10.48	6.21, 9.21
	Median	6.90	6.09	6.01	6.40
	Min, Max	3.23, 19.69	2.73, 19.24	1.66, 21.47	1.66, 21.47
	% ≥ 0.12 µg	100%	100%	100%	100%

Statistical summary of DNA yields (µg) from samples used to assess aliquot-to-aliquot reproducibility

Total DNA Yield (µg/aliquot) Acceptable Minimum = 0.12 µg	**N**	70
	Mean ± SD	7.97 ± 4.07
	95% CI of Mean	7.00, 8.94
	Median	7.29
	Min, Max	2.61, 19.24
	% ≥ 0.12 µg	100%

Statistical summary of lot-to-lot microbial community consistency results

Min CV (%)	0.22
Max CV (%)	21.95
Mean CV (%)	5.84
Median CV (%)	4.92
Total data points	156
Overall pass rate (CV ≤ 30%)	100%

Statistical summary of aliquot-to-aliquot microbial community consistency results

Min CV (%)	0.62
Max CV (%)	32.48
Mean CV (%)	5.69
Median CV (%)	4.74
Total data points	156
Overall pass rate (CV ≤ 30%)	99.4%

e. *Whole Microbiome Analysis Studies*

The primary objectives of the study were to:

- Demonstrate that the whole microbiome is stable during storage at room temperature in the range of 20-26°C in the OMD-200 device for up to 30 days.
- Demonstrate that the OMD-200 device preserves the representation of the *in vivo* state of the whole microbiome (i.e., "snap-shot" or neutrality), where the *in vivo* state is characterized as unstabilized fecal samples collected and processed immediately.
- Demonstrate the performance reproducibility of the OMD-200 device for the whole microbiome across multiple device lots (lot-to-lot) when used to collect from the same fecal sample and across multiple aliquots (aliquot-to-aliquot) of the same OMD-200 collected fecal sample.

Sequencing data generated during the execution of the Stability and Neutrality Study and the Reproducibility Study were leveraged for this analysis. The results presented in this report are intended to expand on the Microbiome Panel results from the OMD-200 validation to include the whole microbiome. The use of the Microbiome Panel in establishing the device claims allowed assessment of the performance of the OMD-200 collection device using clearly defined limits for Microbiome Panel species, which were established during the Whole Genome Sequencing (WGS) Assay Verification Study.

The samples were analyzed to obtain classified read counts for each Microbiome Panel species from control samples and test samples. Classified read counts were rarefied to 2 million reads per sample to account for technical variability in loading samples for sequencing. After rarefaction, the read counts from test samples were then compared, species-by-species, to the control samples to ensure that the test sample read counts were within a defined, acceptable range. The acceptable range was determined based on Test Sample Read Count Limits (TeSaRCol). The use of such an assay was needed to validate the candidate device in order to detect changes between test and control conditions with very specific and well-defined thresholds. Data for adult and pediatric cohorts were evaluated separately.

Data Analysis:
Counts data were transformed using the center-log ratio (CLR) for analysis. Differences in the microbiome between test conditions were evaluated using the Aitchison distance for group wise comparisons, and ALDEx2 differential analysis to evaluate changes between individual taxa. All data analysis, visual representations, and statistical analyses were performed using R. For each analysis objective, the differences in the microbiome were evaluated with three primary criteria:

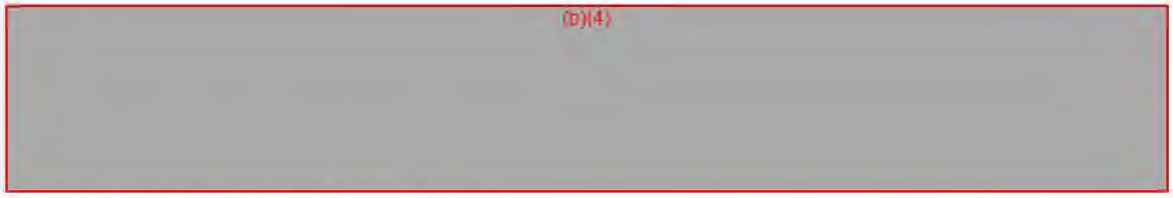
- The Aitchison distance was used to measure the difference in total bacterial microbiome composition and relative abundance between paired samples (e.g., between samples collected with OMD-200 at baseline and the same samples at T60), and between comparison groups of paired samples. (b)(4)

(b)(4)

(b)(4) . Additionally, the variability of the distance values within groups were compared. In each case, magnitude and variability of change were compared to donor-to-donor differences. For comparisons between groups, a Kruskal-Wallis H test (non-parametric) was applied. Two group comparisons were compared with a t-test from baseline to the test group.

- Differential relative abundance analysis was performed on every pass-filter species-level taxon within the sample using ALDEx2. Taxa were considered differentially abundant if the fold-change exceeded the maximum within-condition variance (effect size > 1), and statistically significant (Benjamini-Hochberg adjusted P-value < 0.1) by Welch's paired t-test. Data are represented in an effect plot for visualization of differential relative abundance (between condition) vs. dispersion (within-condition variability).
- Alpha diversity was measured by Shannon's index, and number of observed taxa was quantified after rarefaction to 2 million reads per sample. Differences in alpha diversity between conditions were measured with a paired t-test.

Stability and Neutrality Studies (Whole Microbiome):



Stability (Whole Microbiome) Results:
Group wise comparison of the Aitchison distance using the Kruskal-Wallis H test and a two-group t-test showed no difference between each stability time point ($P > 0.05$), and that the change in microbial profile was significantly lower than observed donor-to-donor differences ($P < 0.0001$; both adult and pediatric cohorts). The observed magnitude of change across time points (Aitchison distance) and the variability within each time point was much less than between donor changes, suggesting that the whole microbiome was stable for up to 30 days at room temperature with or without OM-LQR.

A group wise comparison of Aitchison distance for the stability validation dataset was conducted for an adult cohort and pediatric cohort. Each donor sample was compared at baseline (T0) to the same sample after storage at room temperature with (RTL) or without (RT) liquefaction reagent (OM-LQR) for 30 days (T30). The magnitude of change (distance) and the variability for each time point group is far lower than the between-donor change, suggesting that the microbiome profiles are stable over time. A Kruskal-Wallis non-parametric test was applied between groups, and two-group comparisons using a t-test from RT-T30 vs the remaining groups.

Differential abundance analysis was performed across all storage conditions in comparison to the baseline (OMDB) samples. For all conditions, no taxa had a differential abundance exceeding the measured within group variance and therefore no significant changes in taxa were detected (effect size < 1, adjusted P-value > 0.1). This indicates that the differences between these conditions did not exceed the inferred sample variability within the group.

A: Adult Cohort

B: Pediatric Cohort

Neutrality (Whole Microbiome) Results:
Group wise comparison of the Aitchison distance using the Kruskal-Wallis H test and a two-group t-test showed that the change in microbial profile was significantly lower between OMD-200 collected fecal samples at baseline (OMDB) and unstabilized control fecal samples at baseline (CB) than that observed for donor-to-donor differences at baseline ($P < 0.0001$; shown below for both adult and pediatric cohorts). This suggested that the OMD-200 device maintained the representation of the fecal sample at the point of collection.

A: Adult Cohort **B: Pediatric Cohort**

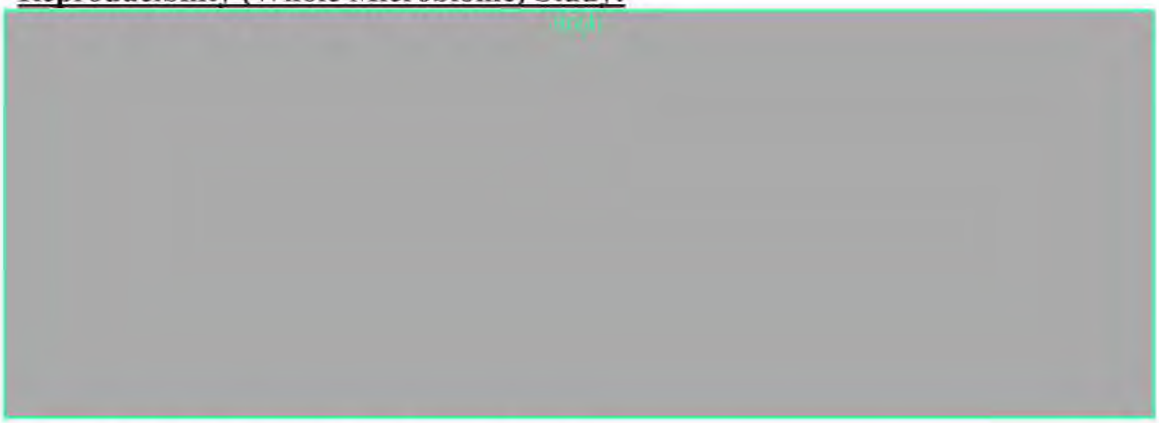
(b)(4)

Differential abundance analysis was performed between OMD-200 collected fecal samples (OMDB) and unstabilized control fecal samples (CB). No taxa had a differential abundance exceeding the measured within-group variance and therefore no significant changes in taxa were detected (effect size < 1, adjusted P-value > 0.1) (shown below for both adult and pediatric cohorts). This indicated that the differences between these conditions did not exceed the inferred sample variability within the group.

A: Adult Cohort **B: Pediatric Cohort**

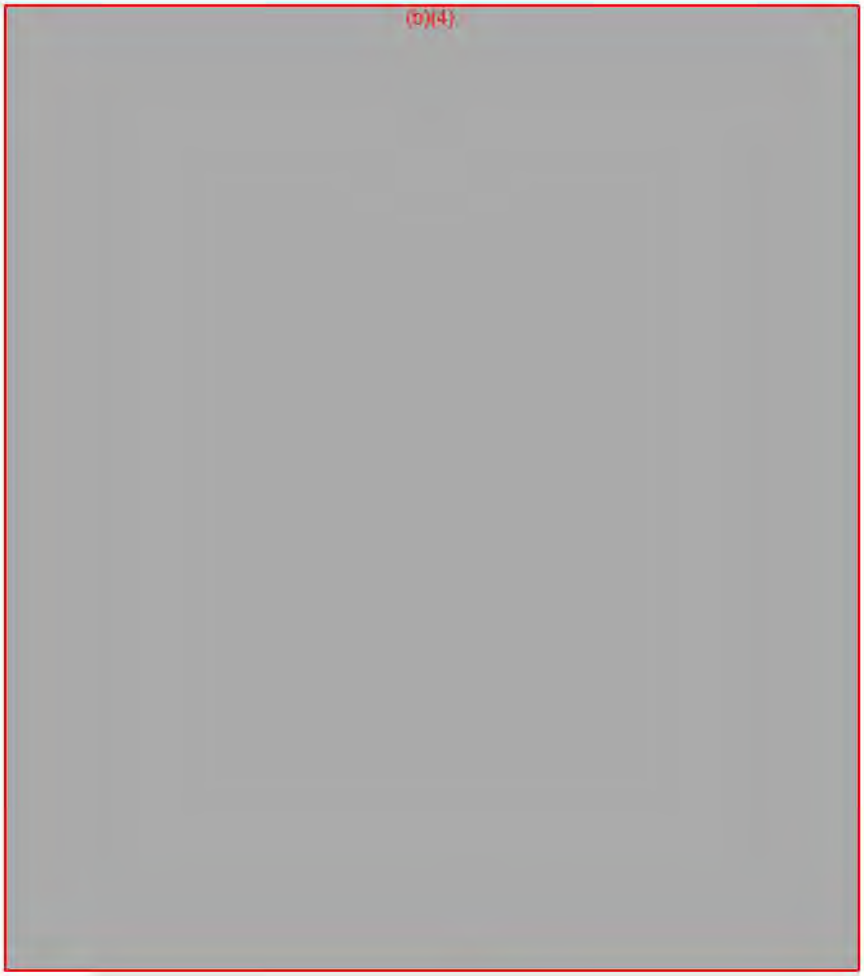
PCA analysis (both adult and pediatric cohorts) and hierarchical cluster analysis of the data showed intra-donor clustering, regardless of collection and storage condition.

Reproducibility (Whole Microbiome) Study:



Reproducibility (Whole Microbiome) Results:
Group wise comparison of the Aitchison distance using the Kruskal-Wallis H test and a two-group t-test showed that, as expected, the difference between the same fecal sample collected into (b)(4) OMD-200 collection devices (lot-to-lot) was significantly lower than the difference between stability time points (30 days). Furthermore, the difference between (b)(4) aliquots extracted from a single OMD-200 collected fecal sample (aliquot-to-aliquot) also showed smaller changes in Aitchison distance compared to the stability time points (30 days) (Figure below).

Significant change ($P < 0.05$) was observed between the same fecal sample collected into (b)(4) OMD-200 collection devices (lot-to-lot) and (b)(4) aliquots extracted from a single OMD-200 device (aliquot-to-aliquot) and the observed magnitude of change and the variability for the lot-to-lot and aliquot-to-aliquot cohorts was much less than between donor changes, indicating that the OMD-200 device provided a reproducible sample collection ($P < 0.0001$).


(b)(4)


(b)(4)

(b)(4)

A compositional principal component analysis of the reproducibility dataset was generated. The first two components explaining the most variance in the data were PC1 23.28% and PC2 with 17.94% variance explained (41.22% in total). Data showed intra-donor clustering on the first two components, regardless of condition (aliquot-to-aliquot replicates and lot-to-lot replicates).

2. Comparison Studies:

   a. *Method Comparison:*

   Method comparison is not applicable for a nucleic acid collection and stabilization device. The device itself does not provide a result that can be used in making a clinical decision. Bench testing studies were done to determine the ability of OMNIgene•GUT Dx to stabilize bacterial DNA from fecal samples.

   b. *Matrix Comparison:*

   Not applicable

3. Clinical Studies:

   Not applicable

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   Not applicable.

M. Instrument Name

Not applicable

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 _____ or No _____X___

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 _____ or No ____X____

   Hazard Analysis and software development are not applicable to this class of device:

3. Specimen Identification:
   Collection devices are not intended to identify specimens. The device itself does not provide a result that can be used in making a clinical decision. Collection devices are intended to preserve and stabilize nucleic acids.

4. Specimen Sampling and Handling:
   See section L.1.b regarding specimen stability.

5. Calibration:
   Not applicable.

6. Quality Control:
   Not applicable.

O. Other Supportive Instrument Performance Characteristics Data Not Covered in the "Performance Characteristics" Section above:

Not applicable

P. Proposed Labeling:

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

Q. Identified Risks to Health and Mitigation Measures:

Identified Risks to Health	Mitigation Measures
Failure to correctly operate the device leading to inadequate sample collection.	Certain labeling information, including warnings and device descriptions. Certain design verification and validation studies.
Failure to stabilize microbial nucleic acid resulting in an inaccurate assay result.	Certain design verification and validation studies.
Device use with unvalidated or incompatible assays leading to inaccurate assay results and improper patient management.	Certain labeling information, including warnings, device descriptions, and study information.
Malfunction of the collection device may lead to possible exposure to infectious pathogens by laboratorians or individuals collecting fecal samples.	Certain labeling information, including warnings and device descriptions.

R. Benefit/Risk Analysis:

Summary	
Summary of Benefit(s)	• OMNIgene•GUT Dx is intended for the non-invasive collection of human fecal samples and the stabilization of DNA from the bacterial community for subsequent assessment of the microbiome profile by an assay validated for use with OMNIgene•GUT Dx. • OMNIgene•GUT Dx facilitates accurate analysis of the relative distribution of different bacteria in the fecal microbiome by standardizing sample collection and stabilization of bacterial nucleic acids during sample storage and transport to the laboratory. This may facilitate the development of fecal microbiome assays by eliminating the need for assay manufacturers to independently develop separate devices for sample collection/nucleic acid stabilization, as well as potentially allowing assay developers to leverage the validation studies performed for OMNIgene•GUT Dx in the development of their assay.
Summary of Risk(s)	• Inaccurate assay results may occur due to failure to stabilize bacterial nucleic acids. • OMNIgene•GUT Dx use with assays that have not been validated for use with this device may lead to inaccurate test results with the potential for patient harm, depending on the assay being used with OMNIgene•GUT Dx. • Malfunction of the collection device may lead to possible exposure to infectious pathogens by laboratorians or individuals collecting fecal samples. • Failure to operate the device correctly may lead to inadequate sample collection, which may lead to inaccurate test results with the potential for patient harm, depending on the assay being used with OMNIgene•GUT Dx.
Conclusions Do the probable	The probable benefits of the OMNIgene•GUT Dx device outweigh the potential risks in light of the listed special controls and applicable general controls.

benefits outweigh the probable risks?	The proposed special controls will help to reduce the risk of device errors and failures. Failure to correctly operate the device, leading to inadequate sample collection, is mitigated by special controls for labeling and certain design verification and validation studies, as well as by current laboratory practices. The risk of the device not sufficiently stabilizing microbial nucleic acid, resulting in inaccurate assay results, is mitigated by special controls requiring certain design verification and validation studies during device development. The labeling special controls, including device description and inclusion of appropriate warnings in the device labeling, will reduce the risk of use with incompatible or unvalidated assays and that malfunction of the collection device may lead to possible exposure to infectious pathogens by laboratorians or individuals collecting fecal samples. The OMNIgene•GUT Dx validation studies provided, including those required by the special controls, suggest that the device will be safe and effective if used as directed by the package insert.

S. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

T. Conclusion:

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code: QPO

Device Type: Device to preserve and stabilize relative abundances of microbial nucleic acids in clinical samples.

Class: II

Regulation: 21 CFR 866.2952