Package Insert
PyloPlus® UBT System
Breath Test for Detection of *H. pylori*
In vitro Diagnostic Medical Device
For Prescription Use Only

SECTION 1. PACKAGE INSERT

This package insert includes information for conducting the *H. pylori* breath test using PyloPlus® UBT (Urea Breath Test) System for analysis with the PyloPlus UBT Kit and PyloPlus® UBT Analyzer.
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SECTION 2. INTENDED USE

The PyloPlus® UBT system is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adults and pediatric patients ages 3-17 years old. The PyloPlus® UBT system consists of the PyloPlus® UBT Kit and the PyloPlus® UBT analyzer. The analyzer is an infrared Spectrometer used for the measurement of the ratio of 13CO2 to 12CO2 in breath samples. The PyloPlus® UBT system is for use by trained health care professionals as prescribed by a physician.

Caution: U.S. Federal Law restricts this device to sale by or on the order of a physician.

SECTION 3. SUMMARY AND EXPLANATION

Since the isolation of the spiral urease-producing *Helicobacter pylori* (*H. pylori*) bacteria in 1983 by Drs. Marshall and Warren, a significant amount of evidence is now present, indicating that the bacteria are an important pathogen in the upper GI tract of humans. *H. pylori* is associated with a number of GI conditions including chronic gastritis, peptic ulcer disease, and varying degrees of dyspepsia. Methods available for detecting current infection of the human stomach by *H. pylori* are generally divided into two (2) general types: Invasive and Non-invasive.
Invasive methods are so named because they include, as a first step, an esophagogastroduodenoscopy ("EGD") with collection of gastric biopsies. These biopsies are then examined by one or more detection methods: histological examination of stained tissue, microbiological culture of the organism, or direct detection of urease activity in the tissue. Biopsy based methods are expensive, entail some patient risk and discomfort and may give false negative results due to sampling errors or when colonization of the gastric mucosa is patchy.
Non-invasive methods include serological testing, fecal antigen test, and urea breath test. Several serological tests that detect serum antibodies to *H. pylori* are commercially available. A positive result with a serologic test cannot distinguish between current infection and past exposure to infection and, therefore, is not a conclusive indicator of current gastrointestinal colonization by *H. pylori*. Urea breath tests are a noninvasive method for detecting current *H. pylori* infection.
13C-urea breath tests provide a non-invasive and non-hazardous analysis of the exhaled breath. The PyloPlus® UBT (described in the next section) measures the 12CO2 and 13CO2 components of the exhaled breath before and after the oral ingestion of 13C-enriched urea. This establishes the baseline ratio of 13CO2/12CO2 and the post ingestion ratio of 13CO2/12CO2 determine the Delta Over Baseline (DOB) (change in the 13CO2/12CO2 ratio).

SECTION 4. PRINCIPLES OF THE PYLOPLUS® UBT

4.1. PRINCIPLE OF THE TEST

The PyloPlus® UBT non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of 13C-enriched urea; it is used to identify those patients with *H. pylori* infection.
The PyloPlus® UBT breath test is performed as follows: a 75 mg 13C-urea powder and 3.0 g citric acid flavoring powder are dissolved in water, and the resulting solution is ingested by the patient. The presence of the citric acid creates an acidic environment in the stomach and delays the transfer of the ingested solution to the duodenum. These two characteristics facilitate the decomposition of the urea by *H. pylori*, if present. Thus, in the presence of urease associated with gastric *H. pylori*, 13C-urea is decomposed to 13CO2 and NH3 according to the following equation:

2(13C-urea) + 2(H2O) → 2(13CO2) + 2(NH3)

13CO2 is absorbed into the blood and then exhaled in the breath. Absorption and distribution of 13CO2 is fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the 13CO2 occurs immediately after the solution is ingested and enables immediate detection of increased 13CO2 in the exhaled breath of *H. pylori*-positive patients. Analysis of the breath
samples is performed by the PyloPlus UBT analyzer (Infrared Spectrophotometer) located at a medical facility. In the absence of gastric *H. pylori*, the 13C-urea does not produce 13CO2 in the stomach because there are no enzymes that can decompose the urea in the stomach.

4.2. DESCRIPTION OF THE PYLOPLUS® UBT DIAGNOSTIC DRUG COMPONENT

The diagnostic drug component of the kit is 13C-urea, a synthetic urea contained in a granulated powder for reconstitution with potable water to provide a clear solution for oral administration. The carbon in the drug component is predominantly Carbon-13, a stable, naturally occurring, nonradioactive isotope of carbon; the relative abundance of Carbon-13 is greater than or equal to 99% in the synthetic drug component. Each dose of 13C-urea is supplied in a polyethylene-lined foil pouch and contains 75 mg of 13C-urea. 13C-urea is the diamide of 13C-carbonic acid and is highly soluble in water (1 gram per mL at 25°C). It has the following chemical formula: 13CH4N2O. An average adult body normally contains about 9 grams of urea, which is a product of protein metabolism. Urea in the body is referred to as natural isotopic abundance urea since it is composed of 98.9% 12C-urea and 1.1% 13C-urea.

SECTION 5. WARNINGS AND PRECAUTIONS

1. For *in vitro* diagnostic use only. The reconstituted 13C-urea powder and the citric acid flavoring solution are taken orally as part of the diagnostic procedure.
2. In the case of accidental overdose – drink water and call the physician.
3. A negative result does not rule out the possibility of *H. pylor*i infection. False negative results can occur with this procedure. If clinical signs suggest *H. pylori* infection, retest with a new sample or an alternate method.
4. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmanni*.
5. A false positive test could occur in patients who have achlorhydria.
6. Antimicrobials, Proton Pump Inhibitors and bismuth preparations are known to suppress *H. pylori.* Ingesting these medications within two weeks prior to performing the breath test may produce false negative test results.
7. If particulate matter is visible in the reconstituted 13C-urea powder and the citric acid flavoring solution after mixing for 30 seconds, the solution should not be used.

8. The following are potentially interfering substances typically found in a patient's breath that were not tested using the PyloPlus UBT System to determine their effect on the test results. The potential sources considered were:
• Mouthwash
• Chewing gum
• Carbonated beverages
• Cigarette smoke
• Acetone (to simulate the effect of ketone production that may result from some diets)
• Alcohol

SECTION 6. SHELF LIFE AND STORAGE
The PyloPlus UBT Kit should be stored at 15°-30°C (59°-86°F) with an expiration date of 36 months. Do not use beyond the expiration date stated on the label.

SECTION 7. INSTRUMENTS
The PyloPlus UBT analyzer (infrared spectrophotometer) is required for analysis of breath samples. For detailed information on the PyloPlus® UBT analyzer, reference the Operator's Manual.

SECTION 8. PATIENT PREPARATION
1. The patient should have fasted at least 1 hour before administering the PyloPlus UBT Kit.
2. The patient should not have taken antimicrobials or Proton Pump Inhibitors within 2 weeks prior to administering the PyloPlus UBT. If PPIs are used within 2 weeks of testing, false negative test results may occur, and the test should be repeated 2 weeks after discontinuation of PPI treatment. A positive result for a patient on PPI could be considered positive and be acted upon.

SECTION 9. BREATH COLLECTION AND PREPARATION
9.1 Materials provided in each PyloPlus UBT Kit:
• One (1) pouch of 13C-urea powder
• One (1) packet of citric acid flavoring
• Test instructions
• One (1) Quick Reference Instructions (QRI)
• Two (2) breath collection bags, one (1) blue bag for the BASELINE sample and one (1) red bag for the POST-sample.
• One (1) drinking straw
• One (1) sample transport bag
9.1.2 Materials needed but not provided
• A 15-minute timer
• Potable water

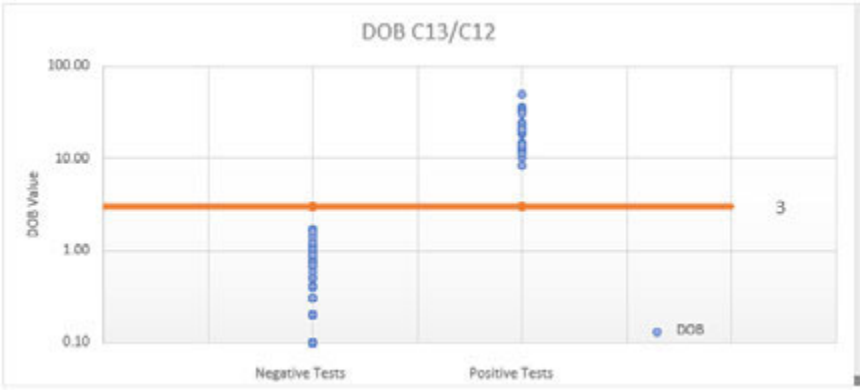
9.2 Step-By-Step Procedure
Time intervals listed in the following step-by-step procedure are critical.
9.2.1 Verify that the patient has been prepared for the test as specified in Section 8. above.
9.2.2 Open the PyloPlus UBT Kit, which should contain all the materials listed in Step 9.1. Label each breath collection bag to maintain patient identification using a felt tip permanent marker, or according to your laboratory or office procedure.
9.2.3 Collect the BASELINE breath sample according to the following steps:
a) Pick up the blue breath collection bag.

b) Remove the twist-off cap from the mouthpiece of the breath collection bag.
c) Instruct the patient to: (1) breathe normally; (2) take a deep breath then hold their breath for 10 seconds; (3) partially exhale in the room, before fully exhaling into the mouthpiece of the bag.
d) Replace the cap firmly on the mouthpiece of the bag.
Note: *If the patient has not held their breath for 10- seconds or does not fill the bag completely, there is a possibility a test result will not be obtainable.*
Note: *The bag is not fully closed if the cap does not click into place. Not fully closing the bag my cause the breath sample to slowly leak out.*
9.2.4 Prepare the 13C-urea solution no more than 50 minutes before administering it to the patient. Urea slowly decomposes in water.
a) Pick up the citric acid flavoring packet and tear open. Place contents of citric acid flavoring packet into 13C-urea pouch by tearing open the pouch and carefully pouring contents of the citric flavoring packet into the open 13C-urea pouch.
b) Add approximately 100 ml drinking water (about 1/3 full) to the 13Curea pouch.
c) Close the Ziplock feature of the 13C-urea pouch securely and shake the mixture for up to 30 seconds.
d) Instruct the patient to drink all of the drug solution with the straw provided directly from the 13C-urea pouch, without stopping. Advise the patient NOT to 'rinse' the inside of his/her mouth with the drug solution before swallowing. Discard the straw after the patient has finished drinking the drug solution.
9.2.5 Set the timer for 15 minutes. The patient should sit quietly and should not eat, drink or smoke during the 15-minute interval.
9.2.7 After 15 minutes have elapsed, pick up the red (pink) breath collection bag. Collect the POST-SAMPLE breath sample according to the procedure described in Steps 9.2.3 b through 9.2.3 d.
9.2.8 Store the specimens at 15°-30°C (59°-86°F) until analysis is performed.
9.2.9 Perform breath sample analysis within 7 days of breath sample collection. If desired, use the plastic sample transport bag for transport of the breath samples.

SECTION 10. QUALITY CONTROL
Complete operating information, including self-diagnostic instrument routines and user maintenance procedures provided in the Instruction manuals for the PyloPlus UBT analyzer. Additionally, each office laboratory or test facility should follow its own internal procedures for quality control.

SECTION 11. TEST RESULTS
11.1 The Test Method
The ratio of 13CO2 to 12CO2 in breath samples is determined by the PyloPlus UBT analyzer (an Infrared Spectrophotometer).
11.2 Calculation of Results
The result is provided as the Delta over Baseline (DOB) which is the difference between the ratio of 13CO2/12CO2 in the POST-DOSE sample and the corresponding ratio in the BASELINE sample. No calculations are required by the user.
11.3 Determination of the Cutoff Point
The cutoff point is the value used to discriminate between *H. pylori*-infected and uninfected individuals. The Delta Over Baseline cutoff point was confirmed to be 3.0 in a controlled study of 115 adult patients (30 infected and 85 uninfected). The cutoff point was confirmed by comparing the PyloPlus® UBT test result (DOB) positive and negative patients, to the composite reference standard (pathology, rapid urease, and culture when available). The 115 adult patients used for the cutoff study are the first 115 of the total 316 prospectively enrolled patients from the pivotal study.

Figure 1 below shows the PyloPlus® UBT test cutoff point graphically, which distinguishes *H. pylori*-positive and negative patients.



11.4 INTERPRETATION OF RESULTS
A PyloPlus® UBT test result of equal to or greater than 3.0 Delta Over Baseline is interpreted as diagnostically positive, indicating the presence of urease associated with *H. pylori*. A PyloPlus® UBT test result of less than 3.0 Delta Over Baseline is interpreted as diagnostically negative, indicating the absence of urease associated with *H. pylori*.

The 3.0 DOB cutoff point applies to both initial diagnosis and post treatment (eradication) monitoring of *H. pylori* infection. For more details, refer to section 12.

SECTION 12. LIMITATIONS OF THE TEST
12.1 Post treatment monitoring of *H. pylori* should be performed after at least four weeks of treatment for *H. pylori* infection. Earlier assessment may give false results.
12.2 Safety and effectiveness in patients under the age of 3 years have not yet been established.
12.3 The specimen integrity of breath samples and reference gases stored in breath bags under ambient conditions has not been determined beyond 7 days.
12.4 A correlation between the number of *H. pylori* organisms in the stomach and the PyloPlus® UBT test results has not been established.
12.5 Data is insufficient to recommend the use of this test on pregnant and lactating women.

SECTION 13. EXPECTED VALUES
Delta Over Baseline values, as determined by the PyloPlus UBT System from the pivotal clinical study, reported 63 positive and 250 negative results from the prospectively enrolled population. The negative results had a DOB range from 0-2.9. The positive results had a DOB range of 3.4-90.5 A histogram of the distribution of Delta Over Baseline values from pre-therapy positive and negative patients is shown in figure 2A and 2B.

Figure 2A. Distribution of Data for Pre-Therapy Negative Patients as Determined in the Pivotal Clinical Study

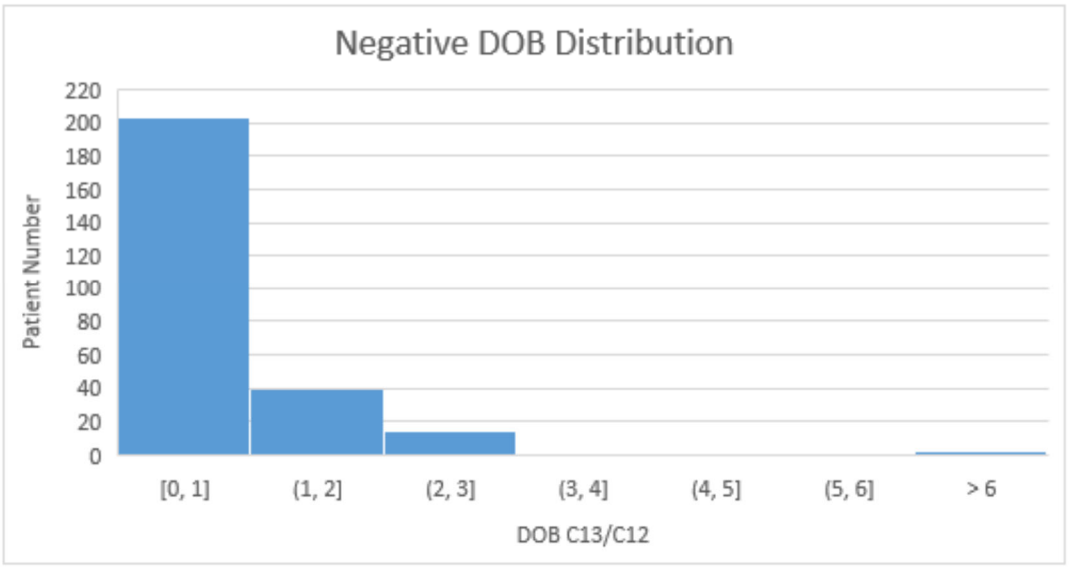
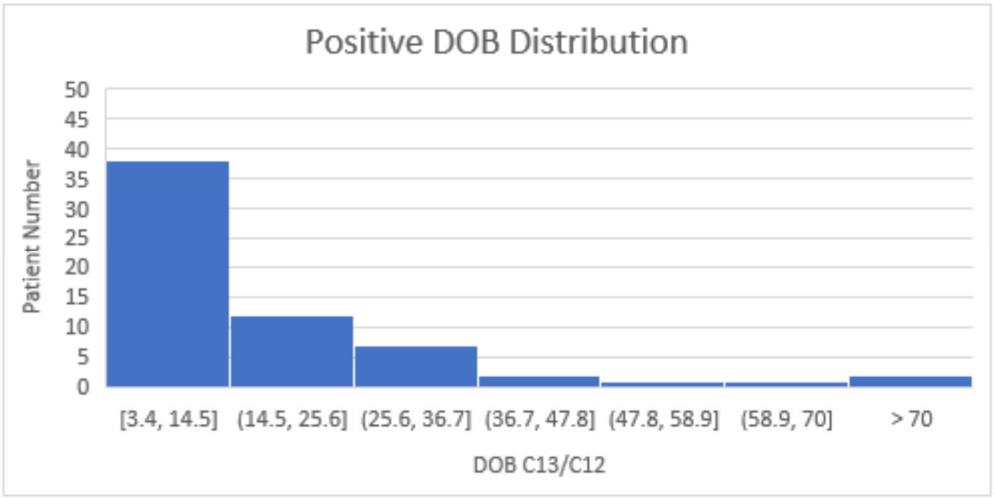


Figure 2B. Distribution of Data from Pre-Therapy Positive Patients as Determined in the Pivotal Clinical study



SECTION 14. PERFORMANCE CHARACTERISTICS

14.1. The primary outcome measure for clinical validation of the PyloPlus UBT is a composite reference method consisting of culture (when available), histology, and rapid urease test.

***14.*2 For** analytical Performance Characteristics for the PyloPlus UBT analyzer, refer to the Analyzer Instruction Manual.

14.3 Clinical Performance in Clinical Trials.

14.3.1 Pre-Therapy

Experimental Design

The data presented here was collected from a prospective, non-randomized, open-label, pivotal clinical trial, designed to assess the sensitivity and specificity of the PyloPlus® UBT compared to EGD biopsy in determining the status of gastrointestinal infection with *H. pylori* (pretherapy phase). There were 316 adult pre-therapy patients at 6 USA based sites including 1 USA based reference laboratory. Patients were evaluated by at least two of three diagnostic methods:

1. Histopathology: Biopsy specimens, fixed with 10% buffered formalin, were cut into 4 mm sections stained with Giemsa stain, and examined by an experienced pathologist.
2. Rapid Urease Test: Biopsy specimens were tested for urease activity with an FDA-cleared test according to the package insert.
3. H. pylori culture (when available): Biopsy specimens were sent to a USA based laboratory for culture analysis.

Results

The results are presented in two-way contingency tables. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistic.
The analysis of safety and effectiveness was based on the 316 evaluable patients that had been enrolled over the duration of 16-months. Of the 316 patients who completed the testing, no adverse events were reported. The analysis of safety and effectiveness of the PyloPlus UBT System was assessed by determining the ability of the test to measure active metabolism of urea pre- and post-ingestion of 13C-urea for initial diagnosis of persons suspected of *H. pylori* infections in the stomach. There were 34 patients positive by the CRM and 110 patients determined to be negative by CRM. The analysis contained only congruent results obtained by CRM (histology, rapid urease test and culture when available). The calculated performance is provided in table 1. below. Patients on PPIs (172) are omitted from the primary analysis because of the potential for a false negative result from the CRM.

Table 1. PyloPlus UBT Performance-Primary Analysis

	Composite Reference Method		
ARJ PyloPlus UBT System	Positive	Negative	Total
Positive	34	0	34
Negative	0	110	110
Total	34	110	144

Sensitivity: 100% [95% CI (89.9% - 100%)]
Specificity: 100% [95% CI (97.4% - 100%)]

An additional analysis was performed for the pre-therapy group that included patients who were determined to have been taking PPIs and patients not taking PPI at the time of testing. The analysis contained only congruent results obtained by CRM (histology and rapid urease test). When patients on PPIs (172) were included in the pre-therapy group, there were 64 patients positive by the CRM and 252 patients determined to be negative by CRM. There were 63 true positive results and 250 true negative results, two (2) false positive results and one (1) false negative result when the PyloPlus UBT System was compared to the CRM. The calculated performance is provided in table 2 below.

Table 2. PyloPlus UBT Performance- Additional Analysis

	Composite Reference Method		
ARJ PyloPlus UBT System	Positive	Negative	Total
Positive	63	2	65
Negative	1	250	251
Total	64	252	316

Sensitivity: 98.4% [95% CI (91.7% - 99.7%)]
Specificity: 99.2% [95% CI (97.2% - 98.8%)]

14.3.2 Post-Therapy

Experimental Design

The data presented here was collected from a multi-center, non-randomized, open label study, designed to assess the percent of the PyloPlus® UBT post *H. pylori* treatment. PyloPlus UBT results were compared to stool antigen testing using the previously approved cut-off value of 3 DOB. Enrolled patients had been treated for *H. pylori* within the past 6 months at the time of testing and were tested at least 4 weeks post treatment. A central lab analyzed stool specimens and comparative breath specimens. This study was conducted at 2 clinical sites for which there were 76 evaluable patients.

Results

The results are presented in two-way contingency tables. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence interval of the performance statistic.

The analysis of the safety and effectiveness was based on the 76 evaluable patients that had been enrolled over the duration of approximately 3 months. Of the 76 patients who completed the testing, no adverse events were reported. The calculated performances are provided in tables 3.

Table 3. Comparison of PyloPlus UBT to results from Stool Antigen Test in the adult population.

	Stool Antigen Test		
ARJ PyloPlus UBT System	Positive	Negative	Total
Positive	19	1[2]	20
Negative	7[1]	49	56
Total	26	50	76

[1]Seven (7) of the false negative results were followed up with an FDA reviewed UBT and found to be negative by UBT.
[2]The false positive result was followed up with an FDA reviewed UBT and found to be positive by UBT.

Positive Percent Agreement: 73.1% [95% CI (54.6% - 86.3%)]
Negative Percent Agreement: 98% [95% CI (89.7% -99.7%)]

14.3.3 Pediatrics

Experimental Design Primary Objective

The data presented here was collected from a multi-center, non-randomized, open label study, primarily designed to confirm the safety of the 13C-Urea substrate and flavoring component in the pediatric population. The pediatric safety data in conjunction with the adult initial diagnosis, adult post-therapy testing and efficacy data from pediatric efficacy data below are used to support a pediatric post-therapy

testing claim. The study was conducted at 5 clinical sites for which there were 57 evaluable patients enrolled.

Results
Of the 57 evaluable patients, no adverse events were reported.

Experimental Design Secondary Objective
A secondary efficacy analysis was conducted comparing UBT result to stool antigen results. The efficacy cohort is a subset of the 57 patients used for the safety analysis.

Results
The results are presented in two-way contingency tables. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence interval of the performance statistic.

The analysis of the safety and effectiveness was based on the 40 evaluable pediatric patients that had been enrolled over the duration of approximately 6 months. Of the 40 patients who completed the testing, no adverse events were reported. The calculated performances are provided in tables 4.

Table 4. Comparison of PyloPlus UBT to results from Stool Antigen Test in the pediatric population.

	Stool Antigen Test		
ARJ PyloPlus UBT System	Positive	Negative	Total
Positive	1	4	5
Negative	0	35	35
Total	1	39	40

% Positive Agreement: 100%
% Negative Agreement: 90% [95% CI (76.4% -96.0%)]

14.4. REPRODUCIBILITY AND REPEATABILITY RESULTS
Analytical studies were conducted to evaluate the reproducibility and precision (repeatability) of results when measurements are made by different technicians and/or using different PyloPlus® UBT analyzers, or when testing is done on different days and at different sites.

14.4.1. REPRODUCIBILITY ANALYTICAL STUDY
Three gas isotope pairs were used with Delta Over Baseline (DOB) values of 2.2 (high negative), 3.1 (low positive), and 9.50 (moderate positive). The study was conducted over 5 days at three different sites, with two operators/site to measure the DOB values for samples from each of the three sample pairs. The reproducibility study results demonstrated minimal differences in the standard deviation over different samples for both the operator, the devices and between days. Table 3 summarizes the results of the reproducibility study.

Table 3. PyloPlus Reproducibility

Sample	Average DOB	Metric	Within Run	Between Runs (operator)	Between Days	Between Sites
High Neg 2.2	2.27	SD	0.123	0.000	0.027	0.084
		%CV	5.417	0.000	1.180	3.690
Low Pos 3.1	3.18	SD	0.145	0.046	0.000	0.047
		%CV	4.559	1.442	0.000	1.469
Mod Pos 9.5	9.53	SD	0.144	0.000	0.042	0.000
		%CV	1.513	0.000	0.442	0.000

14.4.2. REPEATABILITY ANALYTICAL STUDY

The study was conducted at one site over 12 days with 2 measurements/day of three gas isotope pairs with DOB values of 2.2 (high negative), 3.1 (low positive), and 9.5 (moderate positive). The reproducibility study results demonstrated minimal differences in the standard deviation over different samples and different days. Table 4 summarizes the results of the repeatability study.

Table 4. PyloPlus Repeatability

Sample	Average DOB	Metric	Within Run	Between Runs	Between Days
High Neg 2.2	2.20	SD	0.077	0.000	0.056
		%CV	3.486	0.000	2.300
Low Pos 3.1	3.15	SD	0.051	0.000	0.048
		%CV	1.633	0.000	1.403
Mod Pos 9.5	9.66	SD	0.100	0.053	0.000
		%CV	1.035	0.546	0.000

14.4.3. CARRYOVER ANALYTICAL STUDY

A carryover study was conducted to evaluate the potential for sample to sample carry-over or cross contamination in the PyloPlus UBT System. Five runs were conducted using contrived gas, each run consisting of 10 tests. Testing consisted of alternating between contrived gas alternating between high negative 2.2 and high positive 29.3. Data from tests 1-10 in each run were used in the analysis.

The standard deviation for either the high negative or the high positive <0.10. The results indicate carryover between 2.2 and 29.3 is not a clinically significant amount. Table 5 summarizes the results of the Carryover study.

Table 5. PyloPlus Carryover

	High Negative 2.2			High Positive 29.3		
Day	**Within-run SD**	**Within-Run Variance**	**Mean**	**Within-run SD**	**Within-Run Variance**	**Mean**
1	0.07	0.030	2.3	0.05	0.002	29.2
2	0.07	0.030	2.3	0.08	0.003	29.3
3	0.05	0.022	2.24	0.007	0.000	29.2
4	0.1	0.043	2.3	0.007	0.000	29.3
5	0.07	0.030	2.3	0.1	0.003	29.2

SECTION 13. BIBLIOGRAPHY

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SYMBOL GLOSSARY

See instructions for use

For single use only

Prescription use only

Do not use if package is damaged

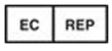
Store at room temperature

In vitro diagnostic device

Manufactured by

Reference number

Made in compliance with CE regulations



European Representative

Distributed by:

Gulf Coast Scientific, Inc.
209 State Street East
Oldsmar, FL 34677
Tel:1-813-855-1557
Fax:1-813-854-2340

e-mail: infro@gulfcoastscientific.com
Website: www.gulfcoastscientific.com

ARJ Medical, Inc.

209 State Street East
Oldsmar, FL 34677

EC REP

Obelis S.A.
Bd Général Wahis
53-1030 Brussels

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PPUBTK-5
PPUBTK-50

CE IVD