CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-586/S-004

CLINICAL AND STATISTICAL REVIEW(S)

Clinical and Statistical Review for New Drug Application # 20-586/Supplement 004

Drug: Pranactin-Citric™ (75 mg ^{13}C-urea and ~ of Citric acid)

Device: BreathTek™ UBT for *H. pylori*
(formerly known as ~ Breath Test for *H. pylori*)

Lead Center: CDRH

Consulting Center: CDER, Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Intended Use: "The BreathTek™ UBT Collection Kit is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes a Gas Isotope Ratio Mass Spectrometer ("GIRMS") for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples."

General Information:

Applicant Name:	Meretek Diagnostics, Inc.
Applicant's Address:	618 Grassmere Park Drive, Suite 20 Nashville, TN 37211
Applicant's Telephone:	(615) 333-6336

Submission/Review Dates:

Date of Submission:	June 13, 2000
Date of Receipt:	July 10, 2000
Date Review Begun:	February 6, 2000
Date Review Completed:	May 1, 2001

APPEARS THIS WAY
ON ORIGINAL

Drug Identification:

Generic Name:	^{13}C-urea and citric acid
Proposed Trade Name:	Pranactin-Citric™
Dosage Form:	75 mg of powder for reconstitution
Route of Administration:	Oral

Related NDAs and 510(k)s:

- Original NDA 20-586 (Meretek UBT): approval September 17, 1996.
- CDRH 510(k) clearance (K972352): October 29, 1997 for the post-treatment monitoring indication
- NDA 20-586, Supplement 002: approval October 29, 1997 for the post-treatment monitoring indication
- CDRH 510(k) clearance (K000316): February 24, 2000 for ~ Breath Test for *H. pylori*.

EXECUTIVE SUMMARY

I. Summary of Clinical Findings

Overview

Generic Name:	^{13}C-urea and citric acid
Proposed Drug Trade Name:	Pranactin-Citric™,
Proposed Device Trade Name:	BreathTek™ UBT for *H. pylori*
Dosage Form:	75 mg of powder for reconstitution
Route of Administration:	Oral

Intended Use: "The BreathTek™ UBT Collection Kit is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes a Gas Isotope Ratio Mass Spectrometer ("GIRMS") for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples."

Pranactin-Citric™ is the formulated drug product of the proposed BreathTek™ UBT. This proposed drug/device is a modification of the currently approved Meretek UBT® Breath Test with Pranactin®. If approved, the BreathTek™ UBT will replace the Meretek UBT® on the market.

A. Efficacy – Phase III Trial

Clinical Reviewer's Comment: The BreathTek™ UBT will be referred to as the [redacted] for the efficacy and safety sections of the review, since this was the name used by the applicant during development.

Data to support the effectiveness of this new drug/device [redacted], are obtained from a single prospective, three-way crossover Phase III trial in 259 adult human subjects in which the performance of the proposed [redacted] test (under fasted and fed conditions) was compared to currently approved version of the test (UBT).

Subjects were eligible if they were asymptomatic or had symptoms of dyspepsia, irrespective of prior ulcer history. All subjects originated from the [redacted] communities. Administration of the tests and other patient-related work was conducted at the [redacted]

The performance data for all evaluable subjects are summarized in the tables below. The relative sensitivity and specificity (95% confidence intervals) for the [redacted] test performed at 1 hour (fed) and 4 hours (fasted) are determined in relation to the UBT. The term "relative" is used to describe sensitivity and specificity since the method for determining the true diagnosis was not endoscopic methods (i.e. the gold standard) but instead the predictive device (standard UBT), which itself has an inherent error rate.

	[redacted] @ 1 hour (fed)		
UBT (standard)	Positive	Negative	Total
Positive	105	1	106
Negative	1	145	146
Total	106	146	252

RELATIVE SENSITIVITY: 99.1% [95% CI (94.9, 100.0)]
RELATIVE SPECIFICITY: 99.3% [95% CI (96.2, 100.0)]

	[redacted] @ 4 hours (fasted)		
UBT (standard)	Positive	Negative	Total
Positive	104	3	107
Negative	1	143	144
Total	105	146	251

RELATIVE SENSITIVITY: 97.2% [95% CI (92.0, 99.4)]
RELATIVE SPECIFICITY: 99.3% [95% CI (96.2, 100.0)]

These results show that the lower limit of the two-sided 95% CI (which equals the lower, one-sided 97.5% limit) is greater than 90% for relative sensitivity and specificity in all cases. Therefore, under both sets of conditions (fed or fasted), the relative sensitivity and specificity of the [redacted] are statistically significantly greater than the protocol-specified threshold of 90%.

The Division recommended to the sponsor on May 17, 1999 that the sponsor should consider a study of 260 subjects (130 *H. pylori* positive and 130 *H. pylori* negative) to rule out a lower bound 97.5% CI of 92%. If these criteria were met, the Division would allow the sponsor to claim that both the fed and fasted states provide acceptable diagnostic performance characteristics. If only one analysis (fed or fasting) satisfied the lower bound of 92% for both relative sensitivity and specificity, then only one method (fed or fasting) would provide acceptable diagnostic performance characteristics.

Clinical and Statistical Reviewers' Comment: Since the applicant has met the criteria for relative sensitivity and specificity under fed and fasted, it is recommended that they be allowed to market the product for use in either the fed or fasted state (i.e., fasting for at least one hour).

B. Safety – Phase III Trial and Post-Marketing Reports

Safety information was obtained from controlled clinical studies, safety of the marketed Meretek UBT (containing Pranactin), and information on each of the components of Pranactin-Citric.

1. Three controlled clinical trials have been conducted with Meretek UBT tests. There have been no adverse events reported in clinical trials conducted with the standard UBT or the [redacted]

2. The applicant states that there have been no Medical Device Reportable (MDR) events associated with the marketed UBT and no Adverse Drug Experiences (ADE) clearly attributable to the Pranactin component of the UBT.

Clinical and Statistical Reviewers' Comment: Since the Meretek UBT contains ^{13}C-urea at a higher dose than proposed for the [redacted] the data obtained with the UBT is felt to be applicable to the [redacted]

3. Review of the safety of each of the components of Pranactin-Citric:
   - ^{13}C-urea: the amount in the [redacted] test is 75 mg, which is less than the 125 mg used in the standard UBT
   - Citric acid: the amount in the [redacted] Citric acid is considered a GRAS (Generally Regarded as Safe) food substance in unlimited quantities. Citric acid is a natural component of fruits and is an ingredient in many soft drinks.
   - Mannitol is an "interim" food additive and can cause diarrhea at doses > 20 grams/day. The amount of mannitol in [redacted] < 5% of the amount that may cause diarrhea.
   - Aspartame: Of the components in the Pranactin-Citric formulation, only aspartame may be harmful to potential test subjects or patients due to the phenylalanine it contains. Aspartame is approximately 50% phenylalanine. The [redacted] contains [redacted] of aspartame ([redacted] of phenylalanine). The amount of aspartame in diet soft drinks (e.g. Diet Coke = 188 mg aspartame or 94 mg of phenylalanine per 12 ounce can) exceeds this amount. The product labeling of the [redacted] addresses the potential risk of phenylalanine to test subjects or patients.

C. Special Populations

Pediatric patients (< 18 years) and patients not judged to be in acceptable health, which can be interpreted as including those with renal or hepatic impairment, were excluded from the Pranactin-Citric development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

1. Efficacy

   The relative sensitivity and specificity of the [redacted] test does not appear to be effected by age (<65 years versus ≥ 65 years), gender, or ethnic group (Whites, Blacks, Hispanics and Asians), although the analysis of some of these subgroups is limited by a small sample size. When the [redacted] test administered at 1 hour was compared to the UBT, the relative sensitivity and specificity for these various subgroups ranged from 98.7% to 100% and 98.4% to 100%, respectively.

2. Safety

   Three controlled clinical trials have been conducted with Meretek UBT tests. There have been no adverse events reported in clinical trials conducted with the standard UBT or the UBT Lite. Therefore, differences in age, gender, or ethnic group do not appear to influence the safety profile of these tests.

II. Recommendations

Pranactin-Citric™ when used as part of the BreathTek™ UBT Collection Kit is safe and effective for the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. The recommendation is for approval of Pranactin-Citric 75 mg for this indication.

We agree with the applicant's recommendation that the test can be administered after fasting at least one hour.

Recommended changes to the applicant's draft labeling and can be found in Appendix 1 and have been incorporated into the final label, which is found in Appendix 2.

CLINICAL REVIEW

I. Introduction/Background

Generic Name:	^{13}C-urea and citric acid
Proposed Trade Name:	Pranactin-Citric™
Proposed Device Trade Name:	BreathTek™ UBT for *H. pylori*
Dosage Form:	75 mg of powder for reconstitution
Route of Administration:	Oral

Intended Use: The BreathTek™ UBT Collection Kit is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes a Gas Isotope Ratio Mass Spectrometer ("GIRMS") for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

A. Principle of the Test

H. pylori is a urease-producing gastric bacterium. Since the enzyme urease is associated with the surface of *H. pylori*, colonization of the mucus layer by the bacteria introduces the urease enzyme into the stomach. Normally, the human stomach does not contain the bacteria or the enzyme. In the presence of urease due to gastric *H. pylori* infection, ingested ^{13}C-urea is decomposed to $^{13}CO_2$ and NH_4^+ in the highly acidic environment of the stomach. The $^{13}CO_2$ is absorbed into the blood and then exhaled in the breath. This results in an increase in the ratio $^{13}CO_2/^{12}CO_2$ in a post-dose breath sample compared with a breath sample taken before the ^{13}C-urea was administered. The difference in this ratio between the pre-dose and post-dose specimens is the Delta Over Baseline (DOB, %). A DOB $\geq$ 2.4 is indicative of the presence of *H. pylori* in adults and supported by data from 26 infected and 23 uninfected adult subjects. The approved Meretek UBT was used as the reference standard.

B. Procedure

The approved UBT is administered by having the patient:

- Consume a commercial pudding test meal to inhibit gastric emptying after a 4-hour pre-test fast
- Provide a pre-dose baseline breath sample using a plastic breath collection bag
- Drink a solution of 125 mg of ^{13}C-urea (Pranactin) prepared by dissolving the ^{13}C-urea powder in 75 mL of sterile water (provided in the kit).
- Provide a post-dose breath sample 30 minutes later

With the BreathTek UBT, the breath test is simplified and administration improved by:

- Formulating the ^{13}C-urea as ^{13}C-urea/citric acid/aspartame/mannitol (Pranactin-Citric) dry powder for reconstitution with 120 mL of potable water
- Collecting breath samples directly by blowing through a straw into a sample tube and then capping the tube.
- Reducing the amount of ^{13}C-urea administered from 125 mg to 75 mg. This reduction is made possible by the addition of citric acid.

The purpose of this submission (Supplement 004) is to change the composition of the diagnostic drug product component of the approved Meretek UBT® Breath Test Collection Kit. The diagnostic drug component of the approved kit is 125 mg of ^{13}C-urea (Pranactin®). The modified formulation is called Pranactin-Citric™ and consists of 75 mg ^{13}C-urea, [redacted] of citric acid, and other ingredients.

The original NDA 20-586 was approved September 17, 1996. Other important clearance/approval dates:

- CDRH 510(k) clearance (K972352): October 29, 1997 for the post-treatment monitoring indication
- NDA Supplement 002: approval October 29, 1997 for the post-treatment monitoring indication
- CDRH 510(k) clearance (K000316): February 24, 2000 for ' [redacted] Breath Test for *H. pylori.*

The development plan for this drug, consisting of a single Phase III clinical trial, was agreed upon by the sponsor and the Division at a meeting on February 24, 1998. A protocol for the study was reviewed and comments (May 19, 1999) were sent to the sponsor. The Division recommended a 3-way crossover study where each subject would receive the [redacted] test twice (once fed and once fasted) in addition to the approved UBT. The applicant adopted this study design.

II. Summary of Clinically Relevant Findings from Other Review Disciplines

A. Chemistry

Ingredient	Amount (mg)	Primary Function
^{13}C-urea	[redacted]	[redacted]
Aspartame		
Mannitol		
Citric acid, [redacted]		

No outstanding issues were identified in the chemistry review. For complete details, please refer to Dr. Holbert's review.

B. OPDRA Consult

OPDRA does not recommend the use of the proprietary name, Pranactin-Citric™. The modifier, "Citric", is used to distinguish the proposed product from the currently marketed product, Pranactin®. They believe this modifier, "Citric", is not appropriate for the following reasons:

- The proposed product, Pranactin-Citric, contains the same active ingredient, ^{13}C-Urea, as the currently marketed product, Pranactin. However, Pranactin-Citric contains a different amount of ^{13}C-Urea than the currently marketed product, Pranactin. Pranactin-Citric contains 75 mg of ^{13}C-Urea instead of 125 mg contained in Pranactin. Moreover, Pranactin-Citric contains the inactive ingredients, [redacted] of citric acid, [redacted] of aspartame, and [redacted] of mannitol, not contained in the current product. The citric acid

was added to Pranactin-Citric to "inhibit gastric emptying." Consequently, the amount of ^{13}C-Urea has been decreased from 125 mg to 75 mg. Also, the citric acid "enhances the diagnostic signal."

- The modifier, "Citric", is used to place an emphasis on the citric acid, an inactive ingredient, contained in the proposed product. However, the proprietary name, Pranactin-Citric™, places an emphasis on an inactive ingredient and this is in violation of 21 CFR 201.10 (c) (5):

> "The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation."

Clinical Reviewer's Comment: Although citric acid is usually an inactive ingredient, in the case of the BreathTek™ UBT, it plays an essential role. It reduces the gastric emptying time, thereby allowing a reduction of the amount of ^{13}C-urea in the formulation from 125 mg to 75 mg. For this reason, DSPIDP believes it is acceptable for the applicant to use the propriatary name of Pranactin-Citric™.

C. Description of Clinical Data and Sources

Material Submitted:	1 volume Electronic Data, including Excel files
Material Reviewed:	1 volume Electronic Data, including Excel files

D. Phase III Clinical Data

This submission contains a single, Phase III clinical trial, which was conducted to determine the safety and effectiveness of the Pranactin-Citric drug when used as a component of the *BreathTek™* UBT for *H. pylori* by demonstrating substantially equivalent diagnostic performance of the test to the approved Meretek UBT.

III. Clinical Review Methods

A. Structure of the Review

For the purpose of determining the safety and effectiveness of the Pranactin-Citric drug when used as part of the *BreathTek™* UBT Collection Kit, one US Phase III study was considered pivotal.

B. DSI Audit

A DSI audit was not conducted for this study. The Principal Investigator for the two clinical sites (Houston VA Hospital, Department of Gastroenterology and the St. Luke's Missionary Baptist Church in Galveston, TX) was previously inspected in 1995 (in relation to NDA 50-719, Helidac therapy). No deficiencies were found. The inspection was classified VAI.

C. Financial Disclosure

David Y. Graham, M.D., the Principal Investigator, was a scientific advisor and consultant to Meretek Diagnostics, Inc. for projects related to diagnostic breath tests, including the ^{13}C-Urea breath test for *H. pylori* during the time that the Phase III study was conducted. For these services, Dr. Graham was paid a monthly retainer. [redacted]

Any potential bias that Dr. Graham [redacted] may have contributed to the study was minimal, since they:

- Did not perform or direct analysis of test specimens
- Were not informed of test results during the field trial
- Had no access to results, which were located in a remote, secure database
- Did not perform data analysis
- Did not prepare the interpretation of field trial results
- Did not prepare the Clinical Field Trial report for submission to the FDA

IV. Review of Controlled Clinical Study

Clinical Reviewer's Comment: The BreathTek™ UBT will be referred to as the UBT Lite for this section of the review, since this was the name used by the applicant during development.

A. Efficacy

1. Objective

To determine the safety and effectiveness of the Pranactin-Citric drug when used as a component of the [redacted] Breath Test for *H. pylori* by demonstrating substantially equivalent diagnostic performance of the test to the Meretek UBT Breath Test.

2. Study Population

Two hundred fifty nine (259) asymptomatic or symptomatic dyspepsia subjects were enrolled: 34% male and 66% female; mean (± SD) age 41.3 ± 11.9 years; 33 (13%) Asians, 155 (60%) Blacks, 51 (20%) Caucasians, 19 (7%) Asians and 1 Other.

3. Study Design

This was a prospective, three-way crossover study. Male and females subjects between 18 and 75 years of age were eligible if they were asymptomatic or had symptoms of dyspepsia and judged to be in acceptable health based upon the results of a medical history. Three UBTs were administered in random order to each test subject: the approved UBT once and the [redacted] twice. In one [redacted] arm the pre-test fast was 1 hour and in the other arm the pre-test fast was at least 4 hours.

The diagnostic threshold or cutoff point for both the UBT and [redacted] was determined to be 2.4 Delta Over Baseline (DOB, %). Patients with a DOB ≥ 2.4 were diagnosed as *H. pylori* positive. Patients with a DOB < 2.4 were diagnosed as *H. pylori* negative.

Pre-established acceptability criteria: For each subgroup (fed and fasted), with at least at least 100 *H. pylori* positive and at least 100 *H. pylori* negative subjects, substantial equivalence of the [redacted] to the UBT will be declared if the lower, one-sided 97.5% confidence interval limit of the observed relative sensitivity and specificity are ≥ 90%.

If both the fed and fasted subgroups are determined to have acceptable performance by these criteria, the applicant will claim that solid and/or liquid food may be consumed up to one hour before the [redacted] If only one Food subgroup satisfies these acceptability requirements, the applicant's claim will reflect the corresponding fasting requirements.

Clinical and Statistical Reviewers' Data Validation Methods
Validation of the efficacy data was performed by independently reviewing the electronic data for 100% of the population. The reviewer's assessment of evaluability was the same as the applicant's for all patients.

8. Results - Effectiveness

Of the 259 subjects enrolled, 249 completed all three UBTs. Five (5) subjects were unevaluable because they did not complete the UBT or they did not have results from either [redacted] test. Five (5) other subjects completed the UBT and only one of the two [redacted] tests (2 subjects completed the 1 hour [redacted] test (fed) and 3 subjects completed the 4 hour [redacted] test (fasted). Therefore, there were 252 evaluable [redacted] 1 hour) results and 251 [redacted] (4 hour) results.

The performance data for all evaluable subjects are summarized in the tables below. The relative sensitivity and specificity (95% confidence intervals) for the [redacted] performed at 1 hour (fed) and 4 hours (fasted) are determined in relation to the UBT.

Clinical and Statistical Reviewers' Comment: The term "relative" is used to describe sensitivity and specificity since the method for determining the true diagnosis was not endoscopic methods (i.e. the gold standard) but instead the predictive device (standard UBT), which itself has an inherent error rate. It is possible that the [redacted] and the UBT (standard) may have given some patients the same, but inaccurate, diagnosis since they are essentially the same tests being administered under different conditions. However, the [redacted] has high rates of agreement with the UBT (standard), as evidenced by the > 99% relative sensitivity and specificity in the 1 hour test. Therefore, it is reasonable to expect that the true sensitivity and specificity of the [redacted] is close to that of the UBT (standard), which was previously compared to endoscopy and was shown to have a sensitivity of 95.2% and a specificity of 89.7%.*

** data obtained from the approved Meretek UBT label.*

	[redacted] @ 1 hour (fed)		
UBT (standard)	Positive	Negative	Total
Positive	105	1	106
Negative	1	145	146
Total	106	146	252

RELATIVE SENSITIVITY: 99.1% [95% CI (94.9, 100.0)]
RELATIVE SPECIFICITY: 99.3% [95% CI (96.2, 100.0)]

	[redacted] @ 4 hours (fasted)		
UBT (standard)	Positive	Negative	Total
Positive	104	3	107
Negative	1	143	144
Total	105	146	251

RELATIVE SENSITIVITY: 97.2% [95% CI (92.0, 99.4)]
RELATIVE SPECIFICITY: 99.3% [95% CI (96.2, 100.0)]

These results show that the lower limit of the two-sided 95% CI (which equals the lower, one-sided 97.5% limit) is greater than the protocol-specified threshold of 90% for relative sensitivity and specificity in all cases. Therefore, in accordance with a provision specified in the study protocol, the sponsor concluded that the [redacted] is clinically equivalent to the UBT.

The difference in relative sensitivity and specificity between the two subgroups (i.e., [redacted] at 1 hour (fed) and at 4 hours (fasted)) was not statistically significant ($p > 0.05$ by Fisher's Exact Test). Therefore, since both subgroups demonstrated acceptable performance, solid and/or liquid food may be consumed up to one hour before the [redacted]

Clinical and Statistical Reviewers' Comment: Since both subgroups obtained a lower bound 97.5% confidence interval of 92% or greater, the applicant may claim that both the fed and fasted states provide acceptable diagnostic performance characteristics (based on a previous agreement, May 17, 1999).

Diagnostic discrepancies

There was one false positive result for the [redacted], assuming the UBT (standard) is correct, for both the 1-hour and 4-hour tests in the same subject (253-pound black female). The UBT result was 1.9, while the 1-hour and 4-hour [redacted] results were 3.1 and 3.6, respectively. The patient was not available for follow-up re-testing.

There was one false negative result for the [redacted] assuming the UBT is correct, in the 1-hour test and three false negative results in the 4-hour test obtained from three

patients. All three were black females ranging from 190 to 231 pounds. All were available for follow-up re-testing and the results are shown below.

	Initial Test Results (DOB)			Re-Test Results (DOB)		
Subject ID	**UBT**	**[redacted] 1-hr**	**[redacted] 4-hr**	**UBT**	**[redacted] 1-hr**	**[redacted] 4-hr**
256	2.4	1.8 (FN)	1.0 (FN)	0.5	0.5 (TN)	0.5 (TN)
260	16.2	3.2 (TP)	0.0 (FN)	7.9	1.1 (FN)	1.7 (FN)
266	10.7	10.2 (TP)	1.6 (FN)	40.2	5.3 (TP)	5.7 (TP)

FN= false negative; TP = true positive; TN = true negative

In one patient, approved UBT results changed from positive to negative upon re-testing while the [redacted] results were consistently negative at the 1-hour and 4-hour timepoints. In the other two patients, the initial [redacted] results at 1-hour and 4-hours were inconsistent. Both became negative upon re-testing in one patient and both became positive in the second patient while the approved UBT was consistently positive for both. The explanation for these discrepancies is not readily apparent and may be due to random errors in administration of the test or analysis of test results.

Clinical and Statistical Reviewers' Comment: Although there were 3 black females with discrepant results, in the entire study there were 101 black females with concordant results. Therefore, the performance of the test in this subpopulation appears adequate.

B. Integrated Summary of Safety (ISS)

1. Phase III trial

No adverse events related to administration of the UBT or [redacted] tests were reported or encountered during the trial. A letter from the Principal Investigator (Dr. Graham) was provided by the applicant, which attests to this lack of adverse events.

Clinical and Statistical Reviewers' Comment: We believe this statement to have validity based on post-marketing data, see below.

2. Review of the components of the [redacted]

- ^{13}C-urea: the amount in the [redacted] test is 75 mg, which is less than the 125 mg used in the standard UBT
- Citric acid: the amount in the [redacted] test is [redacted] Citric acid is considered a GRAS (Generally Regarded as Safe) food substance in unlimited quantities. Citric acid is a natural component of fruits and is an ingredient in many soft drinks.
- Mannitol is an "interim" food additive and can cause diarrhea at doses > 20 grams/day. The amount of mannitol in [redacted] < 5% of the amount that has been implicated in causing diarrhea.
- Aspartame: Of the components in the Pranactin-Citric formulation, only aspartame may be harmful to potential test subjects or patients due to the phenylalanine it contains. Aspartame is approximately 50% phenylalanine. The [redacted] contains [redacted] of aspartame (i.e., [redacted] of phenylalanine). The amount of aspartame in diet soft drinks (e.g. Diet Coke = 188 mg aspartame or 94 mg of phenylalanine per 12 ounce can) exceeds this amount. The product labeling of the [redacted] addresses the potential risk of phenylalanine to test subjects or patients.

3. Clinical Trials

Three controlled clinical trials have been conducted with the approved Meretek UBT test. There have been no adverse events reported in clinical trials conducted with the standard UBT or the [redacted]

Test	N	Purpose
Meretek UBT	134	To establish the cutoff point
Meretek UBT	693	To obtain information on the effectiveness for post-treatment monitoring
Meretek UBT vs. [redacted]	259	To validate the test

4. Post-Marketing

The applicant states that there have been no Medical Device Reportable (MDR) events associated with the Meretek UBT and no Adverse Drug Experiences (ADE) clearly attributable to the Pranactin component of the Meretek UBT.

V. Dosing and Administration Issues

The applicant has demonstrated that by including citric acid in the drug component of the test (^{13}C-urea), the dose can be reduced, a mixed-nutrient test meal is no longer necessary, and the sampling time can be reduced from 30 to 15 minutes without altering the diagnostic signal of the test.

VI. Use in Special Populations

The performance data for all evaluable subjects by age, gender, and race are summarized in the tables below. The relative sensitivity and specificity observed in each subgroup were similar to the results for the overall group. Calculation of relative sensitivity and specificity for the [redacted] est performed at 1 hour (fed) and 4 hours (fasted) are determined in relation to the UBT.

	[redacted] @ 1 hour (fed)					
AGE	**< 65 years**			**• 65 years**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	99	1	100	6	0	6
Negative	1	140	141	0	5	5
Total	100	141	241	6	5	11
	RELATIVE SENSITIVITY: 99.0% RELATIVE SPECIFICITY: 99.3%			RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%		
GENDER	**Males**			**Females**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	44	0	44	61	1	62
Negative	0	41	41	1	104	105
Total	44	41	85	62	105	167
	RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 98.4% RELATIVE SPECIFICITY: 99.0%		
RACE*	**White**			**Black**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	13	0	13	71	1	72
Negative	0	36	36	1	77	78
Total	13	36	49	72	78	150
	RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 98.6% RELATIVE SPECIFICITY: 98.7%		
RACE*	**Hispanic**			**Asian**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	10	0	10	11	0	11
Negative	0	9	9	0	22	22
Total	10	9	19	11	22	33
	RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%		

*Race for one patient was recorded as "other". That patient was identified as positive by all three diagnostic tests: UBT standard, [redacted] @ 1 hour and [redacted] @ 4 hours.

	——— ; @ 4 hours (fasted)					
AGE	**< 65 years**			**• 65 years**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	99	2	101	5	1	6
Negative	1	138	139	0	5	5
Total	100	140	240	5	6	11
	RELATIVE SENSITIVITY: 98.0% RELATIVE SPECIFICITY: 99.3%			RELATIVE SENSITIVITY: 83.3% RELATIVE SPECIFICITY: 100.0%		
GENDER	**Males**			**Females**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	43	1	44	61	2	63
Negative	0	41	41	1	102	103
Total	43	42	85	62	104	166
	RELATIVE SENSITIVITY: 97.7% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 99.0% RELATIVE SPECIFICITY: 96.8%		
RACE*	**White**			**Black**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	13	0	13	70	3	73
Negative	0	35	35	1	76	77
Total	13	35	48	71	79	150
	RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 98.7% RELATIVE SPECIFICITY: 95.9%		
RACE*	**Hispanic**			**Asian**		
UBT (standard)	Positive	Negative	Total	Positive	Negative	Total
Positive	10	0	10	11	0	11
Negative	0	9	9	0	22	22
Total	10	9	19	11	22	33
	RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%			RELATIVE SENSITIVITY: 100.0% RELATIVE SPECIFICITY: 100.0%		

*Race for one patient was recorded as "other". That patient was identified as positive by all three diagnostic tests: UBT standard, ——— @ 1 hour and ——— @ 4 hours.

VII. Conclusions and Recommendations

Pranactin-Citric™ when used as part of the *BreathTek™* UBT Collection Kit is safe and effective for the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. The recommendation is for approval of Pranactin-Citric 75 mg for this indication.

We agree with the applicant's recommendation that the test can be administered after fasting at least one hour.

Recommended changes to the applicant's draft labeling and can be found in Appendix 1 and have been incorporated into the final label, which is found in Appendix 2.

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Ruthanna Davi, MS
Office of Biostatistics
Division of Biometrics III

Concurrence:
HFD-590/TLMO/RocaR
HFD-725/TLStat/HigginsK
HFD-590/DivDir/GoldbergerM

cc:
HFD-590/Div File/NDA 20-586/S-004

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ON ORIGINAL

Appendix 1 - Proposed Labeling Changes

CDER Proposed Additional Wording

1. The following sentencehighlighted in gray should be added to the label to clarify that the

Method Comparisons in Clinical Trials

Point estimates of *Percent Agreement* of the Breathtek™ UBT with Meretek UBT® are listed below the contingency table. The comparative method for determining the true diagnosis was the predictive device (Meretek UBT®) rather than endoscopic methods. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistics. The confidence intervals are entered in parentheses following the point estimate of the statistic.

Table 2. Comparison of Breathtek™ UBT (≥ 1-hour fast) with Meretek UBT®

	BreathTek™ UBT Results		
Meretek UBT®	**positive**	**negative**	**Total**
positive	105	1	106
negative	1	145	146
Total	106	146	252

Percent Agreement with Meretek UBT® positive subjects: 99.1 % [95% CI: (94.9, 100.0)]
Percent Agreement with Meretek UBT® negative subjects: 99.3 % [95% CI: (96.2, 100.0)]

CDRH Proposed Additional Wording

1. Section VIII (Quality Control)

Appropriate wording regarding the details of how quality checks are performed, which appears in the Meretek UBT® label, should be added back in to the proposed label.

2. Section IX (Test Results, Determination of the Cutoff Point)

Figure 1 in the Meretek UBT® label (comparing the Meretek UBT® to histology) should be added back in to the proposed label. In addition, a figure representing the results obtained from the study in healthy volunteers comparing the Meretek UBT® to the Breathtek™ UBT should be added.

3. Section XI (Expected Values)

Figure 1 in the Meretek UBT® label (comparing the Meretek UBT® to histology) should be added back in to the proposed label. In addition, a figure representing the results obtained from the study in healthy volunteers comparing the Meretek UBT® to the Breathtek™ UBT should be added.

Appendix 2 – Final BreathTek™ UBT Package Insert (5/09/01)

APPEARS THIS WAY
ON ORIGINAL

I. Intended Use

The BreathTek™ UBT Collection Kit is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *Helicobacter pylori* infection in adult patients. The test may be used for monitoring treatment if used at least four weeks following completion of therapy. For these purposes, the system utilizes a Gas Isotope Ratio Mass Spectrometer ("GIRMS") for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

For administration by health care professionals. To be administered under a physician's supervision.

II. Summary and Explanation

Since the isolation of the spiral urease-producing *Helicobacter pylori* (*H. pylori*) in 1983 by Warren and Marshall[1], a significant body of evidence has accumulated indicating that the bacteria is an important pathogen in the upper GI tract of humans.[2,3] The causal relationship between *H. pylori* and chronic active gastritis, duodenal ulcer, and gastric ulcer is well documented.[4,5]

Methods available for detecting **current** infection of the human stomach by *H. pylori* are generally divided into two general types: *Invasive* and *Non-invasive*. Invasive methods are so called 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 (for example, the CLOtest®). Biopsy based methods are expensive, entail some patient risk and discomfort, and may give false negative results due to sampling errors when colonization of the gastric mucosa is patchy.[6]

The non-invasive, non-radioactive method for detecting **current** *H. pylori* infection is based on the BreathTek™ UBT which is described in the next section.

Several serological tests that detect serum antibodies to *H. pylori* are commercially available. A positive result with these tests cannot distinguish between **current** infection or past exposure to infection and, therefore, is not a conclusive indicator of current gastrointestinal colonization by *H. pylori*.

III. Principle of the BreathTek™ UBT for *H. pylori*

Description of the Pranactin-Citric™ Diagnostic Drug Component

The diagnostic drug component of the kit is ^{13}C-urea, a synthetic urea contained in a granulated powder (Pranactin-Citric™) 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, non-radioactive isotope of carbon; the relative abundance of Carbon-13 is greater than or equal to 99%.

Each three (3) gram dose of Pranactin-Citric™ is supplied in a polyethylene-lined foil pouch and contains 75 mg of ^{13}C-Urea, citric acid[9], aspartame and mannitol.

^{13}C-urea is the diamide of ^{13}C-carbonic acid and is highly soluble in water (1 gram per mL at 25°C). It has the following chemical formula: $^{13}CH_4N_2O$.

An average adult body normally contains about 9.0 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% ^{12}C-urea and 1.1% ^{13}C-urea.

Principle of the Test

In the BreathTek™ UBT for *H. pylori*, 3 g of reconstituted Pranactin-Citric™ containing 75 mg of ^{13}C-urea is ingested by the patient. In the presence of urease associated with gastric *H. pylori*, ^{13}C-urea is decomposed to $^{13}CO_2$ and NH_4^+ according to the following equation:

$$\underset{^{13}\text{C-urea}}{(NH_2)_2{}^{13}CO} + H_2O + 2H^+ \xrightarrow{HpUrease} {}^{13}CO_2 + 2NH_4^+$$

The $^{13}CO_2$ is absorbed in the blood, then exhaled in the breath. This results in an increase in the ratio of $^{13}CO_2$ to $^{12}CO_2$ in a TEST breath sample compared to a BASELINE sample taken before the Pranactin-Citric™ solution was consumed. Analysis of the breath samples is performed by Gas Isotope Ratio Mass Spectrometry ("GIRMS") at Meretek's clinical laboratory or at other qualified laboratories licensed by Meretek Diagnostics, Inc.

The BreathTek™ UBT can detect very low levels of *H. pylori* colonization and, by assessing the entire gastric mucosa, avoids the risk of sampling errors inherent in biopsy based methods. In the absence of gastric *H. pylori*, the ^{13}C-urea does not produce $^{13}CO_2$ in the stomach. The ratio of $^{13}CO_2$ to $^{12}CO_2$ in the TEST breath sample remains essentially the same as the BASELINE.

IV. Warnings and Precautions

1. For *in vitro* diagnostic use only. The Pranactin-Citric™ drug solution is taken orally as part of the diagnostic procedure.

2. Phenylketonurics: Contains Phenylalanine, 75 mg per dosage unit. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of phenylalanine.)

3. A negative result does not rule out the possibility of *Helicobacter pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternate method.

4. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori* and ingestion of these within two weeks prior to performing the BreathTek™ UBT may give false negative results.

5. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii.*

6. Premature TEST breath collection time can lead to a false negative diagnosis for a patient with a marginally positive BreathTek™ UBT result.

7. A false positive test could occur in patients who have achlorhydria.[7]

8. If particulate matter is visible in the reconstituted Pranactin-Citric™ solution after thorough mixing, the solution should not be used.

V. Shelf Life and Storage

The BreathTek™ UBT Collection Kit should be stored at 15°-30°C (59°-86°F). Pranactin-Citric™ has an expiration date. Do not use beyond the expiration date stated on the label.

VI. Patient Preparation

1. Remind the patient that Pranactin-Citric™ contains phenylalanine. Phenylketonurics restrict dietary phenylalanine.

2. The patient should have fasted at least one hour before administering the BreathTek™ UBT.

3. The patient should not have taken antimicrobials, proton pump inhibitors, or bismuth preparations within two weeks prior to administering the BreathTek™ UBT.

VII. Procedure

Materials

Materials provided:

Each single-patient BreathTek™ UBT Collection Kit contains:

- One plastic drinking cup
- Three plastic straws
- One clear plastic specimen return box containing:

  Pranactin-Citric™ powder (3 g)

  Four (4) bar-coded 10 mL breath sample tubes

  A set of three self-adhesive bar-code stickers. All bar-codes should bear the same number.

Materials needed but not provided

- A timer capable of timing an interval up to fifteen (15) minutes.
- Scissors for opening the Pranactin-Citric™ pouch.
- Test request forms and specimen return envelopes are supplied with the kits or are provided separately by your Meretek licensed testing laboratory.

Note: A Gas Isotope Ratio Mass Spectrometer and related analytical equipment are required for analysis of breath samples. Breath sample analyses are performed at Meretek's clinical laboratory or qualified laboratories licensed by Meretek Diagnostics, Inc.

Step-By-Step Procedure

Time intervals listed in the following step-by-step-procedure are critical. They are highlighted by the timer icon: ◷

1. Verify that the patient has been prepared for the test as specified in Section VI.

2. Open the BreathTek™ UBT Collection Kit, which should contain all the materials listed above. Open the clear plastic specimen return box at the arrows indicated by "PULL". Fold back the sides of the plastic box and place on a flat surface so that the four (4) bar coded tubes are presented in a vertical, upright position. Remove the self-adhesive label containing the three (3) peel-off bar-code stickers. Place one peel-off bar-code sticker on the **Lab Copy** of the test request form and one on the **Physician Copy** of the test request form. An extra bar-code sticker is provided if needed. There are two blue-labeled BASELINE sample tubes and two pink-labeled TEST sample tubes.

   The contents of each clear plastic specimen return box are bar-coded to maintain positive patient identification. Verify that the bar-codes on the test request form and tubes match. To avoid confusion, be sure to keep these items patient-specific.

3. Complete all areas of the test request form.

4. Collect two BASELINE breath samples according to the following procedure:

   a. Remove the collection tube stopper.

   b. Insert a new straw to within about 0.5 inch of the bottom of the tube.

   c. Instruct the patient to take a deep breath, pause momentarily, then blow ***gently*** through the straw into the bottom of the tube for about 3 to 5 seconds. *The tube should be held in a near-vertical position during this process.*

   While the patient is blowing through the straw, slowly withdraw the tube and immediately

replace the stopper. *Seat the stopper completely within the rim of the tube and press it down with a slight twisting motion to its original position. Avoid pressing too hard on the stopper as it could break the glass tube.*

Note: Using this procedure, condensed moisture on the inside of the tube indicates the tube has been adequately filled. However, there must be no saliva or sputum in the tube. If mouth fluids accumulate in the tube, discard the tube using biohazard precautions.

5. ◷ Prepare the Pranactin-Citric™ solution *no more than sixty (60) minutes before administering it to the patient. Urea slowly decomposes in water.*

   a. Remove the Pranactin-Citric™ pouch from the specimen return box. Tap the upright packet of Pranactin-Citric™ to settle the contents in the bottom half.

   b. With scissors, cut off the top of the packet and carefully empty the contents into the drinking cup provided, making sure to transfer all of the contents by tapping.

   c. Add potable water to the **FILL LINE** indicated on the outside of the container.

   d. Replace the lid securely and swirl up to *two minutes* to dissolve the packet contents; typically, only one minute is required for complete dissolution. *The resulting solution should be clear with no particulate matter. If particulate matter is present after thorough mixing, the solution should not be used.*

6. Instruct the patient to drink all of the solution with a new straw, without stopping. Advise the patient NOT to 'rinse' the inside of his/her mouth with the solution before swallowing. *Discard the straw as it must not be used for breath collection.*

   ◷ Set the timer for 15 minutes.

7. The patient should sit quietly and should not eat, drink or smoke during the 15-minute interval. When fifteen (15) minutes have elapsed, collect two TEST breath specimens by the procedure described in Step 4 above.

8. Review the test request form for accuracy and completeness, and retain the **Physician Copy** for your records. Verify that the bar-code number on the test request form matches the bar-code number on all breath specimen tubes.

9. Fold the **Lab Copy** of the test request form and put it into the specimen return box or specimen return envelope, as directed by your testing laboratory. Close the specimen return box and put it into the specimen return envelope. Store the specimens at 15°-30°C (59°-86 °F) until shipment.

10. ◷ Send the return envelope to the Meretek clinical laboratory, or other qualified laboratory licensed by Meretek, within three (3) days after the breath samples were collected.

VIII. Quality Control

The Meretek clinical laboratory and other qualified laboratories licensed by Meretek to perform the BreathTek™ UBT analyses follow written policies and procedures for a comprehensive Quality Assurance (QA) program which is designed to monitor and evaluate the overall quality of the total testing process (pre-analytic, analytic and post-analytic).

As part of the QA program, the analytical Quality Control system includes provisions for the detection of persistent and sporadic errors. Persistent analytical errors, which span multiple samples and controls, are detected by analysis of periodically placed control gases in the patient breath sample runs. Control rules with high error detection capability are applied to the control data to accept or reject whole runs or portions of runs. Sporadic errors, which occur unpredictably on individual specimens, are detected by quality criteria applied to each sample tube measurement.

Quality checks are also performed on the final results. For example:

- Each specimen tube must contain at least 1.5 volume percent CO_2 to assure the tube contains adequate breath for analysis. If not, the result is rejected.

- The relative abundance of the BASELINE sample must be within the interval: -27.0 to -17.0 delta per mil. Fasting samples outside this range are highly unlikely and new (backup) specimens should be tested.

- Quality criteria are applied to BreathTek™ UBT results to assure that BASELINE and TEST specimens were collected properly. The DOB result must be greater than -1.0.

In the event that failure of quality criteria on both specimen pairs which have been submitted for analysis precludes reporting a valid test result, you will be notified as soon as possible. The notification on the report form will include the nature of the quality failure (e.g., empty sample tube) and the recommended remedial action.

IX. Test Results

The Test Method

The ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples is determined by Gas Isotope Ratio Mass Spectrometry ("GIRMS") at the Meretek clinical laboratory or qualified laboratory licensed by Meretek Diagnostics, Inc.

Calculation of Results

The result of the BreathTek™ UBT for *H. pylori* is provided as the Delta Over Baseline. No calculations are required by the customer. Delta Over Baseline is the difference between the ratio ($^{13}CO_2/^{12}CO_2$) in the TEST specimen and the corresponding ratio in the BASELINE sample.

Determination of the Cutoff Point

The cutoff point is the level of BreathTek™ UBT result used to discriminate between *H. pylori* infected and uninfected individuals. For the BreathTek™ UBT, the Delta Over Baseline cutoff point was determined to be 2.4 in a controlled study of 26 infected and 23 uninfected adult volunteers. Test subjects were judged to be in acceptable health based on the results of a medical history and physical examination and demonstrated no uncontrolled clinically significant abnormality other than, for some, symptoms of peptic ulcer. The previous version of the Meretek urea breath test, the Meretek UBT®, was used as the reference standard. The cutoff point was calculated by determining the BreathTek™ UBT result level at which negative and positive subjects were best distinguished by co-optimization of relative sensitivity and specificity. The 2.4 cutoff point for the BreathTek™ UBT was verified in an independent study by retrospective analysis of Clinical Field Trial data collected on 145 *H. pylori* negative and 105 *H. pylori* positive test subjects, again using the original Meretek UBT® as reference. Asymptomatic subjects and those with dyspepsia were included in the validation study. Figure 1a shows graphically the BreathTek™ UBT Delta Over Baseline cutoff point which distinguishes *H. pylori* positive and negative subjects.

For the Meretek UBT® Breath Test, the Delta Over Baseline cutoff point was determined to be 2.4 in a controlled study of 66 infected and 53 uninfected asymptomatic, apparently healthy volunteers. Histological examination of biopsy tissue was used as the reference standard. The cutoff point was evaluated by determining the Meretek UBT® Breath Test result level at which histologically negative and positive subjects were best distinguished. Figure 1b shows graphically the Meretek UBT® Breath Test Delta Over Baseline cutoff point which distinguishes histologically positive and negative subjects. Note that in Figures 1a and 1b, the Delta Over Baseline scales are logarithmic.

Figure 1a. Cutoff for BreathTek™ UBT

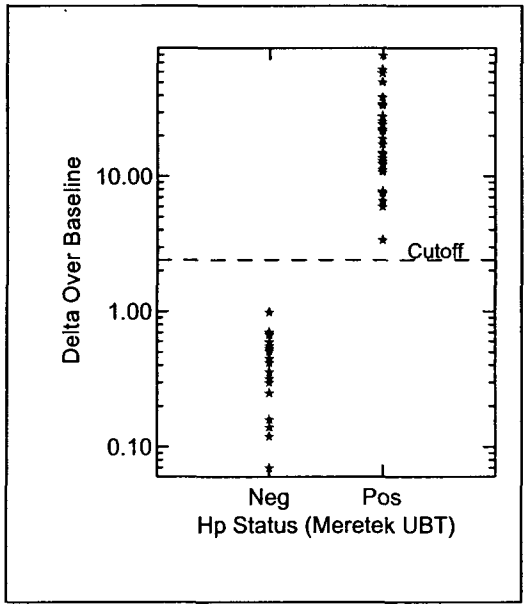
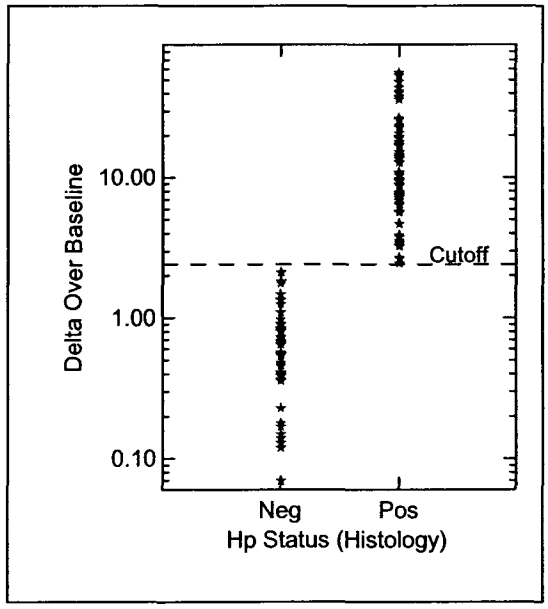


Figure 1b. Cutoff for Meretek UBT®



Interpretation of Results

A BreathTek™ UBT result greater than or equal to 2.4 Delta Over Baseline is interpreted as diagnostically positive indicating the presence of urease associated with *H. pylori*. A BreathTek™ UBT result less than 2.4 Delta Over Baseline is interpreted as diagnostically negative indicating the absence of urease associated with *H. pylori*.

The 2.4 Delta Over Baseline cutoff point applies to both initial diagnosis and post-treatment monitoring of *H. pylori* infection.

X. Limitations of the Test

1. The BreathTek™ UBT should not be used until four weeks or more after the end of treatment for the eradication of *H. pylori*, as earlier post-treatment assessment may give false negative results.

2. The performance characteristics for persons under the age of 18 have not been established for this test.

3. The specimen integrity due to storage of breath samples in collection tubes under ambient conditions has not been determined beyond 20 days.

4. A correlation between the number of *H. pylori* organisms in the stomach and the BreathTek™ UBT result has not been established.

5. The predicate device (Meretek UBT®) was standardized in asymptomatic healthy volunteers and subsequently validated in clinical trials limited to patients with documented duodenal ulcer disease.

XI. Expected Values

Delta Over Baseline values for the BreathTek™ UBT were determined in a controlled clinical study of 26 infected and 23 uninfected adult volunteers. The Meretek UBT® Breath Test was used as the reference method in the diagnosis of infection. The range of BreathTek™ UBT Delta Over Baseline values for the *uninfected* group was determined to be 0.0 to 1.0. A histogram for the distribution of Delta Over Baseline values from the uninfected subjects is shown in Figure 2a.

Values for the Meretek UBT® Breath Test were determined in a controlled clinical study of 66 infected and 53 uninfected asymptomatic, apparently healthy volunteers. Histological examination of biopsy tissue was used as the reference method in the determination of infection in this study. The range of Meretek UBT® Delta Over Baseline values for the uninfected group was determined to be 0.0 to 2.2. A histogram for the distribution of Delta Over Baseline values from the uninfected subjects is shown in Figure 2b.

Figure 2a. BreathTek™ Expected Values

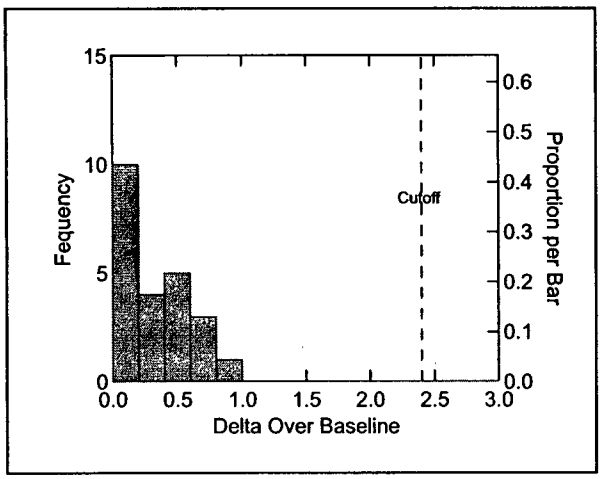
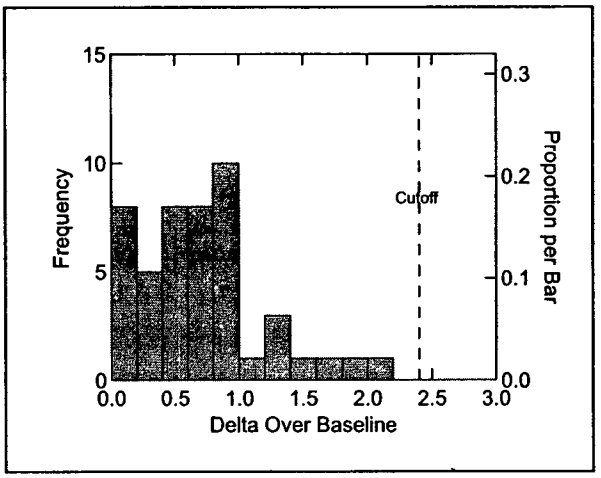


Figure 2b. Meretek UBT® Expected Values



XII. Performance Characteristics

Imprecision of the GIRMS Analytical System

Experimental Design

The experimental design of the GIRMS system imprecision study conformed to the general recommendations of the NCCLS Guideline EP5-A (User Evaluation of Precision Performance of Clinical Chemistry Devices). On each of nineteen test days, each of the three levels of test gases were analyzed three (3) times each. Whenever possible these test specimens were analyzed along with the daily run of patient samples.

Results

For each control level, a nested , one-way analysis of variance was performed to estimate:

- Within-run imprecision, S_{wr}
- Day-to-day imprecision, S_{dd} (corrected)
- Total imprecision, S_t (with Satterthwaite correction)

Statistical results are summarized in Table 1. In the table, each entry represents the standard deviation followed in parentheses by the percent coefficient of variation.

Table 1. Nested Analysis of Variance Results

Imprecision Component	Level 1 Mean = -26.3	Level 2 Mean = -16.7	Level 3 Mean = 119.8
Within-run	0.14 (0.54)	0.10 (0.63)	0.15 (0.13)
Day-to-Day	0.00 (0.00)	0.09 (0.55)	0.08 (0.07)
Total	0.14 (0.54)	0.14 (0.84)	0.17 (0.14)

Method Comparisons in Clinical Trials

A. Comparison of the BreathTek™ UBT with the Meretek UBT®

Experimental Design

The method comparison data presented here were collected from a prospective, cross-over clinical field trial designed to validate the BreathTek™ UBT test procedure and to examine the effect of pre-test fasting time on test performance. The study included 252 adult test subjects from Houston and Galveston, Texas. Subjects were judged to be in acceptable health based on the results of a medical history and physical examination and demonstrated no uncontrolled clinically significant abnormality other than, for some, symptoms of dyspepsia.

Test subjects were tested for *H. pylori* infection using the Meretek UBT® Breath Test according to established procedure and with the BreathTek™ UBT under differing conditions of pre-test fasting times. Otherwise, no special instructions were given to subjects beyond those listed in the step-by-step procedures for administration of the Meretek UBT® and BreathTek™ UBT. To minimize potential bias due to test order, the sequence of urea breath tests administered to each subject was randomized. All breath tests were administered to a given individual within fourteen (14) days of one another, most often, and at a minimum, on successive days.

Results

It was demonstrated in the field trial that the BreathTek™ UBT may be administered at any time beyond one hour after consuming solid and/or liquid food.

Method comparison results are presented in a two-way contingency table below (Table 2).

Point estimates of *Percent Agreement* of the BreathTek™ UBT with Meretek UBT® positive and negative results are listed below the contingency table. The comparative method for determining the true diagnosis was the predictive device (Meretek UBT®) rather than endoscopic methods. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistics. The confidence intervals are entered in parentheses following the point estimate of the statistic.

Table 2. Comparison of BreathTek™ UBT (≥ 1-hour fast) with Meretek UBT®

	BreathTek™ UBT Results		
Meretek UBT®	**positive**	**negative**	**Total**
positive	105	1	106
negative	1	145	146
Total	106	146	252

Percent Agreement with Meretek UBT® positive subjects: 99.1 % [95% CI: (94.9, 100.0)]
Percent Agreement with Meretek UBT® negative subjects: 99.3 % [95% CI: (96.2, 100.0)]

B. Comparison of the Meretek UBT® with endoscopic methods

Experimental Design

The method comparison data presented here were collected from two (2) independent double blind clinical field trials which involved treatment of *H. pylori* infection. The studies included 499 adult patients with duodenal ulcer disease at 75 clinical sites in the United States. Patients were tested for *H. pylori* infection initially (using histopathology, microbiological culture, CLOtest®, and the Meretek UBT®), and at various post-treatment intervals throughout the study (using histopathology, microbiological culture, and the Meretek UBT®). In these clinical trials patients were treated with various combinations of clarithromycin, omeprazole and placebo. Note, however, that there is no evidence that differing treatment regimens affect the performance of the Meretek UBT®.

1. Histopathology

Biopsy specimens, fixed with 10% buffered formalin, were cut into 4-mm sections, stained with Genta stain and examined by an experienced pathologist.

2. Microbiologic culture

Culture was performed using fresh blood-based media, both selective and non-selective, at 37°C in 12% CO_2 in air with 98% humidity. *H. pylori* were identified by Gram stain, typical colony morphology, and biochemical properties (production of oxidase, catalase, and urease).

3. CLOtest® (Delta West, Limited, Bently, West Australia)

A biopsy specimen was tested for urease activity with the CLOtest® according to the instructions in its package insert.

4. The Meretek UBT® Breath Test for *H. pylori*

The diagnostic Meretek UBT® Breath Test was performed in accordance with procedures described in its package insert.

Results

Method comparison results are presented in two-way contingency tables. In tables 3, 4, and 5, the Meretek UBT® Breath Test results are compared with the CLOtest®, histology, and with the combined endoscopic method results (CLOtest®, histology and culture) for the initial patient visit.[8] In table 6, the Meretek UBT® Breath Test results are compared with the combined endoscopic method results (histology and culture) for the post-treatment visits which occurred four weeks or more after end of treatment.

The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistics. The confidence intervals are entered in parentheses following the point estimate of the statistic.

Performance Characteristics for Initial Diagnosis

Table 3. Comparison with CLOtest® for Initial Visit

	Meretek UBT® Results		
CLOtest®	**positive**	**negative**	**Total**
positive	397	31	428
negative	1	16	17
Total	398	47	445

Relative sensitivity: 92.8 % [95% CI: (90, 95)]
Relative specificity: 94.1 % [95% CI: (71,100)]

Table 4. Comparison with Histology for Initial Visit

	Meretek UBT® Results		
Histology	**positive**	**negative**	**Total**
positive	394	20	414
negative	3	27	30
Total	397	47	444

Relative Sensitivity: 95.2 % [95% CI: (93, 97)]
Relative Specificity: 90.0 % [95% CI: (74, 98)]

Table 5. Comparison with combined endoscopic methods for Initial Visit

Combined endoscopic methods used were CLOtest®, histology, and culture per DAIDP guidelines [8] for pre-treatment diagnosis.

	Meretek UBT® Results		
Endoscopy	**positive**	**negative**	**Total**
positive	395	20	415
negative	3	26	29
Total	398	46	444

Sensitivity: 95.2 % [95% CI: (93, 97)]
Specificity: 89.7 % [95% CI: (73, 98)]

Performance Characteristics for Post-Treatment Monitoring

Table 6. Comparison with combined endoscopic methods* for Post-Treatment Visits (four weeks or more after End of Treatment (EOT))

	Meretek UBT® Breath Test results			
	1 Month EOT	3 Months EOT	6 Months EOT	1-6 Months Combined
Endoscopy	pos neg	pos neg	pos neg	pos neg
positive	187 6	123 8	91 5	401 19
negative	5 97	4 87	2 80	11 264
Sensitivity (95% CI)	**96.9** (93,99)	**93.9** (88,97)	**94.8** (88,98)	**95.5** (93,97)
Specificity (95% CI)	**95.1** (89,98)	**95.6** (89,99)	**97.6** (92,100)	**96.0** (93,98)

*Combined endoscopic methods used were histology and culture per DAIDP guidelines [8] for post-treatment monitoring.

Please note that the post-treatment performance characteristics at 1, 3 and 6 months after therapy are not statistically different. Therefore, the single best estimates of sensitivity and specificity are presented in the 1-6 Months Combined column.

Negative Predictive Value (NPV) for Post-Treatment Monitoring

Given the post-treatment sensitivity (95.5%) and specificity (96.0%) observed in these studies, and assuming a treatment efficacy of 90% (10% prevalence of residual *H. pylori* infection), the NPV of the Meretek UBT® is greater than 99%. When efficacy of treatment drops to 50%, the NPV is still greater than 95%.

XIII. Bibliography

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XIV. Name and Place of Business

The BreathTek™ UBT for *H. pylori* Collection Kit is manufactured for Meretek Diagnostics, Inc., Nashville, TN 37211.

XV. Labeling Revision Information

Revision: 09May01

Part Number: 2207


6 SIMPLE, BREATHTAKING STEPS
Directly detect an ACTIVE H. pylori infection
One
Collect baseline breath sample
Two
Prepare the Pranactin-Citric™ solution
Three
Patient drinks Pranactin-Citric™ solution
Four
Collect second breath sample after 15 minutes
Five
Send breath tubes to your testing laboratory
Six
Receive patient results and treat accordingly

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/s/

Renata Albrecht
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for Mark Goldberger, NDA 20-586/S-004