K990931

SEP 24 1999

APPENDIX K

510(k) Summary

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For
Ez-HBT Helicobacter Blood Test

1. SPONSOR/MANUFACTURER

Metabolic Solutions, Inc.
460 Amherst Street
Nashua, NH 03063

Contact Person: David A. Wagner, Ph.D.
President

Telephone: (603) 598-6960

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Date Prepared: March 15, 1999

2. DEVICE NAME

Proprietary Name: Ez-HBT Helicobacter Blood Test

Common/Usual Name: Urea Blood Test for Presence of *Helicobacter pylori*

Classification Name: *Campylobacter pylori*
(Note: *Campylobacter pylori* has been renamed *Helicobacter pylori*.)

3. PREDICATE DEVICES

- PyloriTek Test Kit
  Serim Research Corp.
  K953632

- MERETEK UBT™ Breath Test for H. *pylori*
  Meretek Diagnostics, Inc.
  K952220

4. DEVICE DESCRIPTION

Metabolic Solution's Ez-HBT Helicobacter Blood Test is based on the ability of H. *pylori* to produce the enzyme urease and convert urea to ammonia and carbon dioxide. By providing Helicosol (125 mg of ^{13}C-labeled urea), the carbon dioxide produced by this reaction is carbon-13 labeled and an increase in the level of $^{13}CO_2$ in the blood is an indication of the presence of H. *pylori*.

The test requires a single blood sample, collected 30 minutes after ingestion of the drug. Subsequently, this blood sample is transported to a qualified laboratory. The CO_2 is evolved from the blood into the headspace of the Vacutainer tube and analyzed by gas isotope ratio mass spectrometry (GIRMS) to determine the $^{13}CO_2$:$^{12}CO_2$ ratio. A diagnosis of H. pylori infection is based on the detection of blood $^{13}CO_2$ being greater than a cutoff value.

5. INTENDED USE

The Ez-HBT Helicobacter Blood Test is intended for use in the qualitative detection of urease activity found associated with H. *pylori* organisms colonizing the lining of the human stomach. The test kit will aid in the diagnosis of H. *pylori* infection in adult subjects. The test is performed only by health care professionals and administered under a physician's supervision. A physician will use the Ez-HBT for adult subjects with ulcer symptoms, such as epigastric pain, heartburn, nausea, hematemesis, hematochezia, and melena.

6. SUBSTANTIAL EQUIVALENCE

The Ez-HBT Helicobacter Blood Test and the PyloriTek® have the same basic intended use: to detect the presence of H. *pylori* in human gastric mucosa. The same chemical reaction (the breakdown of urea by means of urease found in the H. *pylori*) is the basis of both tests. When H. *pylori* is present, either through ingestion (Ez-HBT) or by contact (PyloriTek®), hydrolysis of the urea produces CO_2 and NH_4.

In the case of PyloriTek®, the urea hydrolysis reaction takes place in vitro using an endoscopic biopsy and the resulting generation of NH_4 causes a pH change reflected in a color change. In the case of the Ez-HBT, this same reaction takes

place in vivo and results in an increase of $^{13}CO_2$ in the subject's blood. This increase is detected using GIRMS.

A table describing the technological characteristics of these systems follows:

Comparison of Ez-HBT Helicobacter Blood Test
And Predicate Devices

Product Characteristics	Metabolic Solutions Ez-HBT	Serim Research PyloriTek	Meretek Diagnostics UBT Breath Test
Intended Use	Qualitative detection of the presence of *Helicobacter pylori* in the gastric mucosa		
Sample Analyzed	Blood	Tissue Biopsy	Breath
Reagent	^{13}C-Urea	Urea	^{13}C-Urea
Detection Method	GIRMS Detection of excess $^{13}CO_2$ ^{13}C-Urea $\rightarrow$ $^{13}CO_2$	Visual Detection of Urea Degradation: Urea $\rightarrow$ $NH_4^+ \rightarrow$ Color	GIRMS Detection of excess $^{13}CO_2$ ^{13}C-Urea $\rightarrow$ $^{13}CO_2$
Physical Safety	Requires standard venipuncture; No adverse effects reported form the ingestion of ^{13}C-Urea	Requires invasive tissue sampling techniques.	No adverse effects reported form the ingestion of ^{13}C-Urea
Time	35 Minutes	1 Hour	35 Minutes
Temperature	Ambient	Ambient	Ambient
Regulatory Status	Proposed	K953632	K952220

7. PERFORMANCE TESTING

7.1 Pre-Clinical Studies:

7.1.1 Determination of the Cutoff Point in Asymptomatic Controls

A study of 115 adults was conducted to determine the cut-off point of the Ez-HBT. The 95% confidence level for 99% of negative subjects had an Ez-HBT value less than -17.0 delta per mil. This cutoff point was further tested in patients referred for EGD.

7.1.2 Determination of the Cutoff Point in Patients referred for EGD

A study of 121 adult subjects with dyspeptic symptoms and diagnosed for H. *pylori* infection by reference methods (histology and tissue urease testing) was conducted to determine a cutoff point. A receiver operating characteristic (ROC) curve was used to determine the cutoff value for the prediction of H. *pylori* infection. The Ez-HBT test indicated a positive H. *pylori* infection when the blood ^{13}C value at 30 minutes post urea dosing was greater than or equal to -17.0 delta per mil. This cutoff point was further refined in the clinical studies detailed below.

7.2 Clinical Studies

7.2.1 Refinement of the Cutoff Point

In a study of 338 subjects at 7 monitored clinical sites around the United States, the cutoff determination obtained form the preclinical studies was modified. A new cut-off of -17.5 per mil was established by creating Receiver Operating Characteristic (ROC) curves. This change in cut-off, although small, allows the Ez-HBT to be used with maximum efficiency for the qualitative determination of the presence of *Helicobacter pylori*. A secondary outcome of the cut-off modification was the occurrence of an indeterminate zone.

7.2.2 Evaluation of an Indeterminate Zone

The clinical study of 338 patients revealed that a deviation of 0.5 per mil could arise from a variety of sources including air transportation (see below). Therefore, an indeterminate zone of 0.5 per mil around the cutoff (-17.0 to -18.0) was established. Samples in this zone accounted for 4.7% of all samples and are not included in the calculations for sensitivity, specificity and overall accuracy. Samples whose delta value falls into this zone should have the test re-administered and the sample reevaluated.

7.2.3 Evaluation of the Safety and Efficacy of the Ez-HBT test

A clinical study was conducted to evaluate the ability of the Ez-HBT blood test to detect the presence of Helicobacter pylori in the gastrointestinal tract and to evaluate the sensitivity, specificity and accuracy of the Ez-HBT versus reference methods. Three hundred and thirty eight (338) subjects were enrolled at 7 clinical sites. All patients who ingested the ^{13}C-urea solution were included in the safety analysis. Nine (9) patients reported adverse events. None of the events was considered device related. The diagnostic cutoff, expected to be -17.0 delta per mil from a previous pre-clinical trial, was refined to be -17.5 with an indeterminate zone of ± 0.5 delta per mil which excluded 4.7% of the subjects.

Sensitivity, specificity and accuracy were measured versus histology and PyloriTek independently as well as the two methods congruently. The overall sensitivity ranged from 86.4% to 90.2%, specificity ranged from 94.5% to 96.4% and accuracy ranged from 91.0% to 93.8%.

7.2.4 Effect of Air Transportation on Ez-HBT Samples

A study of 20 subjects was carried out to evaluate the effect of air transportation on the Ez-HBT test. Replicate samples were drawn and dispersed randomly into one of three categories:

A) Ground transportation and immediate analysis (GROUND)
B) Ground transportation and analyze only when C arrives (HOLD)
C) Air transportation from New Hampshire to California to New Hampshire and then analysis (AIR)

A comparison between the GROUND samples and the other group reveals no significant effect from the time delay ($\sim$ 1 day). A comparison between the HOLD samples and the AIR samples revealed differences of $\cong$ 1.0 per mil. Since the test has an indiscriminant zone of ± 0.5 per mil, the finding is not considered significant and the effect of air transport of the samples is negligible.

7.3 Non-clinical Studies:

7.3.1 Timing of Blood Collection

The optimal drawing time after administration of the 13C-urea was determined to be 30 minutes. This timing maximized the ability of the Ez-HBT to discriminate between positive and negative subjects while minimizing the duration of the test.

7.3.2 Volume of Blood Required for the Test

Multiple replicate samples were prepared and aliquoted into 1.0, 2.0, 2.5 and 3.0 ml collections. Samples were analyzed over a 14 day period. The volume of blood collected had no significant effect on the delta ^{13}C per mil value (results within ± 1.0 per mil). No significant differences between blood volumes were observed over a 14 day period.

7.3.3 Integrity of Blood Samples under Stress

Blood samples were exposed to a variety of environmental conditions including freezing, refrigeration, heat and room temperature for 7 days. The mean differences from the initial values were generally less than 1 delta per mil. Based on this data, the stability of the blood samples when kept at room temperature is 7 days.

7.3.4 Reproducibility of Measurements

Four (4) replicates were generated from 10 subjects (5 H. ***pylori*** positive and 5 H. ***pylori*** negative) and analyzed on the same day. The mean standard deviation on these measurements was ≅ 0.5 delta per mil (and no more than 1 per mil) for two standard deviations about the mean.

7.4 Conclusions

The clinical studies demonstrate that the Metabolic Solutions, Inc. Ez-HBT Helicobacter pylori blood test performs comparably to other diagnostic methods (e.g., PyloriTek) currently available for the presence of H. *pylori*. The system is safe (no adverse events related to the drug or device were reported during the clinical trials) and thereby has a distinct advantage over other invasive methods such as PyloriTek, which require biopsy. The non-clinical studies indicate that the Ez-HBT blood test performs reliably under anticipated conditions of collection, transportation and storage.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 24 1999

David A. Wagner, Ph.D.
President
Metabolic Solutions, Inc.
460 Amherst Street
Nashua, New Hampshire 03063

Re: K990931
Trade Name: Ez-HBT Helicobacter Blood Test
Regulatory Class: I
Product Code: MSQ
Dated: July 12, 1999
Received: July 13, 1999

Dear Dr. Wagner:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act). You may, therefore, market the device, subject to the general controls provisions of Act. However, you are responsible to determine that the medical devices you use as components in the kit have either been determined as substantially equivalent under the premarket notification process (Section 510(k) of the act), or were on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. Please note: If you purchase your device components in bulk (i.e., unfinished) and further process (e.g., sterilize) you must submit a new 510(k) before including these components in your kit. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, FDA will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

In addition, we have determined that your device kit contains Helicosol™ (125mg ^{13}C-urea lyophilized powder) which are subject to regulation as a drug.

Our substantially equivalent determination does not apply to the drug component of your device. We recommend you first contact the Center for Drug Evaluation and Research before marketing your device with the drug component (NDA 21-092). For information on applicable Agency requirements for marketing this drug, we suggest you contact:

Mark Goldberger, M.D., M.P.H.
Director, Division of Drug Labeling Compliance (HFD-310)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-2366

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act, may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven I. Gutman, M.D. M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K990931

Device Name: Ez-HBT Helicobacter Blood Test

Indications for Use:

The Ez-HBT™ Helicobacter Blood Test is intended for use in the qualitative detection of $^{13}CO_2$ in whole blood specimens, collected after the ingestion of ^{13}C-urea. Helicobacter pylori (*H. pylori*) organisms colonizing the lining of the human stomach, produce urease which converts ^{13}C-urea into $^{13}CO_2$ and ammonia (NH_4^+). The device is indicated as an aid in the diagnosis of *H. pylori* infection in symptomatic adult subjects, 18 years or older. For use by health care professionals. Administer test under a physician's supervision. Metabolic Solutions, Inc. or a qualified laboratory using Gas Isotope Ratio Mass Spectrometry or equivalent instrumentation must analyze the test samples.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NECESSARY)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dubose

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K990931

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)