SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name:	Automatic Glucose Biographer
Device trade name:	GlucoWatch® G2 Biographer
Applicant's name and address:	Cygnus, Inc. 400 Penobscot Drive Redwood City, CA 94063
PMA number:	P990026/S008
Date of Panel recommendation:	None (see Section XI)
Date of notice of approval to the applicant:	August 26, 2002

The original Biographer was approved for adults only, age 18 and older, on March 22, 2001. This supplement is to expand the indications for use to children and adolescents, age 7 -17.

II. INDICATIONS FOR USE

- The GlucoWatch G2 Biographer is a glucose monitoring device indicated for detecting trends and tracking patterns in glucose levels in adults (age 18 and older) and children/adolescents (age 7 to 17) with diabetes. This device is intended for use by patients at home and in health care facilities. The device is for prescription use only.

- The GlucoWatch G2 Biographer is indicated for use as an adjunctive device to supplement, not replace, information obtained from standard home glucose monitoring devices.

- The Biographer is indicated for use in the detection and assessment of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions. Interpretation of Biographer results should be based on the trends and patterns seen with several sequential readings over time.

III. DEVICE DESCRIPTION

The GlucoWatch® G2 Biographer (the Biographer) is a device that provides frequent, automatic, non-invasive glucose measurements. The glucose sample is obtained directly through intact skin. The device is worn like a wristwatch, and is used with a single-use disposable component, the AutoSensor, which attaches to the back of the Biographer and contacts the skin. Each AutoSensor provides the user with up to six glucose measurements per hour over a 13- hour measurement period, giving up to 78 readings per wear. The frequent readings provide the user with trends and patterns in their glucose profiles.

For each wear period, the user attaches a new AutoSensor to the Biographer and applies the device to the forearm or wrist. An adhesive on the AutoSensor and a watchband keep the device

in place. After a 2- hour warm-up period, the device is calibrated with the result from a traditional blood glucose monitor. After calibration, the device automatically measures glucose for up to 13 hours. The user can display the most recent readings on the Biographer and can scroll back through previous readings to get information on glucose patterns.

The Biographer works differently than standard blood glucose meters (i.e., the Biographer measures glucose in interstitial fluid rather than blood). As a result, individual Biographer readings can differ substantially from blood glucose measurements taken at approximately the same time. These individual differences can be somewhat unpredictable and should be taken into account when interpreting results. Because it takes a few minutes to obtain the glucose sample and process the data, the readings obtained by the Biographer are approximately 15 minutes behind a theoretical corresponding blood measurement. On occasion, certain conditions, such as profuse sweating or large temperature fluctuations, can cause a reading to be skipped and the Biographer will not provide a reading. Certain problems (i.e., heavy perspiration, dislodging the Biographer from the skin, high frequency of skipped data points) may cause the Biographer to discontinue glucose monitoring before the end of the 13-hour monitoring period.

The device has high and low glucose alarm settings that may be set by the user (as directed by their health care team) to warn of high or low glucose levels, and an automatic alarm for rapidly decreasing glucose levels. A display provides a readout for time and date, glucose measurements, and a trend arrow to indicate whether the glucose has increased or decreased from the last reading. The user can use the System Check Sensor to check that the Biographer electronics are working correctly and may perform a QC Test to evaluate the condition of a box of AutoSensors. The Biographer contains memory for approximately 4000 readings.

The GlucoWatch G2 Biographer contains the electronics to control the iontophoretic current (used to extract the glucose sample) and biosensor functions, a clock, and connectors to the AutoSensor. The power source is a single AAA battery, with an internal rechargeable lithium back-up battery. The Biographer also contains a temperature sensor to monitor the temperature near the user's skin, and two metal probes to monitor the skin conductance (directly related to the user's perspiration level). User control is via four push buttons located on the face panel.

The AutoSensor contains biosensor and iontophoresis electrodes, hydrogel disks, and a skin adhesive to hold it securely to the skin. Each AutoSensor is individually packaged in a hermetically sealed pouch, which is opened just prior to use and discarded after use.

The Biographer obtains the glucose sample through a process known as reverse iontophoresis, the application of a very low level of electrical current across the skin. The glucose is extracted into the hydrogel disks in the AutoSensor. Glucose reacts with the enzyme glucose oxidase, contained in the hydrogel disks, to form hydrogen peroxide. The hydrogen peroxide reacts on a platinum biosensor to produce an electric current, which is read by the Biographer electronics. This current signal is processed by the Biographer and the signal is translated into an equivalent blood glucose level by a data conversion algorithm.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

None

Warnings

- The device is not designed to replace a regular blood glucose meter. The GlucoWatch G2 Biographer must be used with a traditional blood glucose meter.

- Do not ignore symptoms that may be due to low blood glucose or high blood glucose. The Biographer may not detect every instance in which your glucose levels are too high or too low. If you have symptoms that do not match the Biographer readings, use your regular blood glucose meter to check the Biographer results.

- Do not change your treatment decisions based only on results from the Biographer. For example, some people use a blood glucose test result to help determine an insulin dose before each meal. This is often called a "sliding scale". If you use a sliding scale, be sure to confirm the Biographer result with your regular blood glucose meter to make sure you take the right amount of insulin.

- Do not make fundamental changes in your treatment program without talking to your health care team. Serious illness or accidents may result.

- Remember that Biographer readings can differ from finger-stick test results. When it is time to make an important decision, the Biographer should not be used as a substitute for a finger-stick test. The Biographer must be used with finger-stick blood testing. Then you can make the best treatment decisions and reduce the chance of problems.

Precautions

- Always do the Biographer calibration step carefully. Skipping this step or entering a wrong number into the Biographer may cause faulty results. Follow the instructions for using your regular blood glucose meter. If you question the reading from your regular meter that you plan to use for calibration, repeat the blood glucose test.

- Be sure to set the Low Glucose Alert level 20 to 30 mg/dL above the blood glucose level that you want to make sure is detected. For example, if you want to detect a level of 60 mg/dL, you should set the Low Glucose Alert at 80 or 90 mg/dL. Otherwise, the GlucoWatch Biographer may miss some low blood glucose events and the alarm will not sound.

- Parents and guardians should read the User's Guide and supervise use of the Biographer by their children/adolescents (age 7 to 17). You should understand the benefits and limitations of the Biographer. You should think about any risks involved with unsupervised use of the device by your child (eg, while at school) and make appropriate preparations for such use.

- Always check the last few readings in the Biographer memory to see the current trend in your glucose levels. One reading cannot tell you how fast your glucose levels are changing. If you question the Biographer results, confirm the Biographer readings with your regular blood glucose meter.

- Do not place the Biographer at any site where you have skin irritation left from a prior use. The Biographer should only be placed on sites with normal, healthy skin. Avoid

sites with skin abnormalities such as eczema, cuts, sunburn, or scarring. Skin irritation may be worse than normal.

- Patients with suspected allergies to medical adhesives should consult their health care professional before using the Biographer.

- Do not use an expired AutoSensor. Check the expiration date on the package label before use.

- Do not share your Biographer with another person. This will help prevent spreading infections.

Caution:

- U.S. federal law restricts the GlucoWatch G2 Biographer and AutoSensors to sale by or on the order of a physician.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Periodic glucose self-monitoring using home blood glucose meters will provide information regarding variations in glucose levels.

VI. MARKETING HISTORY

This device has been marketed in the United States since April 15, 2002. A similar device has been marketed in the United Kingdom (UK) since October, 2000.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The use of the GlucoWatch Biographer may cause skin redness, and/or itching after use. Occasional blisters may be observed. Symptoms are usually completely resolved within one to two weeks. People with sensitive skin may experience more intense, but still temporary, redness or itching.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

Refer to the SSED for the approved PMA (P990026) for the summary of pre-clinical studies.

IX. SUMMARY OF CLINICAL STUDIES

A controlled clinical study was conducted to evaluate the performance of the GlucoWatch in a juvenile population (age 7 – 17). In order to evaluate the data from this study, the statistical analysis of the data was based on a comparison of the Biographer values to matching fingerstick glucose meter results taken within a narrow time window. The time window was defined relative to each Biographer reading in order to create comparable data. In order to assess the results of the clinical study data effectively, several important points should be kept in mind:

- The Biographer produces iontophoretic measurements of glucose levels every 10 minutes. For this clinical study, one fingerstick meter value was taken each hour. This

level of testing is far in excess of what is generally performed by even the most diligent of patients with diabetes. Thus, analysis of the data considers the performance of the device compared to as many as 11 fingerstick values per 12-hour monitoring period. However, the actual utility of the Biographer should be compared to the amount of information available with standard clinical practice of 1 to 4 fingersticks per day.

- The consistency and precision of the device are demonstrated by the fact that successive values (every 10 minutes) almost always follow a logical change sequence representative of expected physiological changes in glucose levels *in vivo*. Furthermore, the Biographer plots closely match the direction and speed of changes reflected in the blood glucose data. Again, a more representative assessment of utility should be compared to the amount of information available to patients from the 1 to 4 daily measurements generally available from home meter use.

- Because only one blood measurement was made each hour, only one-third of the data produced by the Biographer could be assessed by the accuracy measures employed in the statistical summaries of performance. Also, it was experimentally difficult to ensure that the user would consistently perform the fingersticks at the correct time. This difficulty was due to the parameters of the clinical study. Many Biographer measurements that would have continued to provide information to the user could not be included in the analyses solely due to the design of the experiment. Examination of the individual time plots for each subject showed that these intermediate results, not used in the analyses, are very consistent with the surrounding points (preceding and succeeding measurements) which were used in the analyses.

- The sponsor has chosen to use the most conservative comparison methods available in the statistical analyses. No data points were excluded as being an outlier from any of the performance analyses.

A. Study Design, Patient Assessment, Demographics

The study of safety and effectiveness of the GlucoWatch G2 Biographer in a juvenile population was performed at two study centers. Study design, objectives, and demographic data are summarized in Table 1. Subjects studied were 7 – 17 years of age with type 1 diabetes requiring treatment with insulin. Subjects were excluded if they had any significant wounds or injuries at the Biographer wear site, had hypoglycemia requiring assistance within the past 6 months, or had congestive heart failure or vascular procedure in the last 6 months. Additionally, subjects were excluded if they had known hepatic failure or adrenal insufficiency or had a hematocrit value outside the range specified in the comparative meter's labeling. The subjects wore up to two Biographers on their forearms. Blood glucose measurements were taken by finger-stick every hour. The subjects stayed at the study site during the wear period (to ensure availability for blood glucose testing) but had unrestricted activity. Study duration was 15 hours with skin evaluations at device removal and at 36, 60, and 84 hours after device removal. Additional skin assessments were performed as needed until all visible irritation was resolved. The reported values from the device were masked from the subjects, so that the measurements would not be used to make any clinical decisions during the study. Subjects and their parents provided written informed consent.

Table 1. Design and Objectives for the Study of Safety and Effectiveness in Juveniles (age 7 – 17)

Study Name	Study in Juveniles
Primary objective	Determine accuracy in a home simulated setting
Hypothesis tested (Basic Design)	Null hypothesis: Estimated bias (defined as difference from the y=x line to the Deming linear regression line) was ≤ 15 mg/dL at 50 or 80 mg/dL or that bias ≤ 15% at 100, 150 and 200 mg/dL. Alternative hypothesis: Estimated bias (defined as difference from the y=x line to the Deming linear regression line) was > 15 mg/dL at 50 or 80 mg/dL or that bias > 15% at 100, 150 and 200 mg/dL.
Comparative device	HemoCue analyzer
Calibrating device	HemoCue analyzer
Duration of use	1 day (15 hours)
Number of Clinical Sites	2
Number of Subjects	
Safety population	66
Efficacy population	66
Number of Biographers	
Safety population	96
Efficacy population	87[a]
Demographics	
Age (years)	
Mean	11.3
SD	3.0
Race (%)	
Asian	2
Caucasian	92
Hispanic	2
Other	5
Gender (%)	
Female	50
Male	50
Diabetes Type (%)	
Type 1	100

[a] 9 Biographers could not be included in theefficacy population because of insufficient paired glucose values for analysis

B. Data Analysis and Results

Biographer readings were compared to blood glucose (BG) tests performed once per hour. The central assessment of the accuracy of the Biographer was based on the estimated bias (defined as the difference from the y = x line to the Deming linear regression line) at five medical decision levels of glucose (50, 80, 100, 150, and 200 mg/dL). The 99% confidence intervals around the bias for all five medical decision levels were within ± 15mg/dL (%) thresholds showing that bias estimates were significantly smaller than those thresholds. The null hypothesis was not rejected, thus the hypothesis that the bias was smaller than the prescribed limits throughout the range was accepted.

1. Detection of Trends and Patterns in Glucose Levels

The GlucoWatch G2 Biographer readings closely matched the direction and speed of changes reflected in the blood glucose data. The median per Biographer correlation coefficient was 0.95.

The clinical utility of detecting trends and patterns in glucose levels is seen with an analysis of the alert capabilities of the device. It is important to set the alert levels in a conservative fashion. Thus, the Low Glucose Alert level should be set above the level at which detection of low blood glucose is required, and the High Glucose Alert level should be set below the level at which detection of high blood glucose is required.

For the Low Glucose Alert, results were analyzed using a definition of hypoglycemia as a BG measurement of 70 mg/dL or below on the comparative device. At a Low Glucose Alert level of 100 mg/dL, 96% (53/55) of the events of hypoglycemia were detected by the Biographer. In addition, the Biographer correctly identified the absence of hypoglycemia on 73% (502/687) of the occasions when BG was greater than 70 mg/dL. Greater detection of hypoglycemia can be obtained by setting the Low Glucose Alert level higher. Data are presented in Table 2.

Table 2. Events of Hypoglycemia Detected by the Biographer

	BG ≤ 70 mg/dL	**BG > 70 mg/dL**
Biographer reading ≤ 100 mg/dL	53	185
Biographer reading > 100 mg/dL	2	502
Total	55	687

To assess Biographer detection of hyperglycemia, study results were analyzed using a definition of BG ≥ 240 mg/dL. At a High Glucose Alert level of 180 mg/dL, 85% (104/123) of the events of hyperglycemia were detected by the Biographer. In addition, the Biographer correctly identified the absence of hyperglycemia on 84% (518/619) of the occasions when BG was less than 240 mg/dL. Data are presented in Table 3.

Table 3. Events of Hyperglycemia Detected by the Biographer

	BG ≥ 240 mg/dL	**BG < 240 mg/dL**
Biographer reading ≥ 180 mg/dL	104	101
Biographer reading < 180 mg/dL	19	518
Total	123	619

2. Agreement Between Individual Biographer Readings and Blood Glucose Test results

Different methods are required to evaluate the performance of this non-invasive device than those used to assess standard BG monitoring systems. Typically, a single capillary whole blood sample is the source for glucose measurements by two comparative systems: the investigational device and a standard laboratory analyzer. In studies of the Biographer, the time-averaged transdermal glucose readings were compared to capillary BG readings taken at specific time points. These differences in sample source and timing of reading impact the interpretation of study results.

Blood glucose measurements were taken at specific times so that they could be "paired" with Biographer readings for analysis. Agreement was analyzed using all the paired glucose measurements in the study. For each data pair, the difference between the Biographer reading and the BG measurement was calculated as a percentage of the BG value.

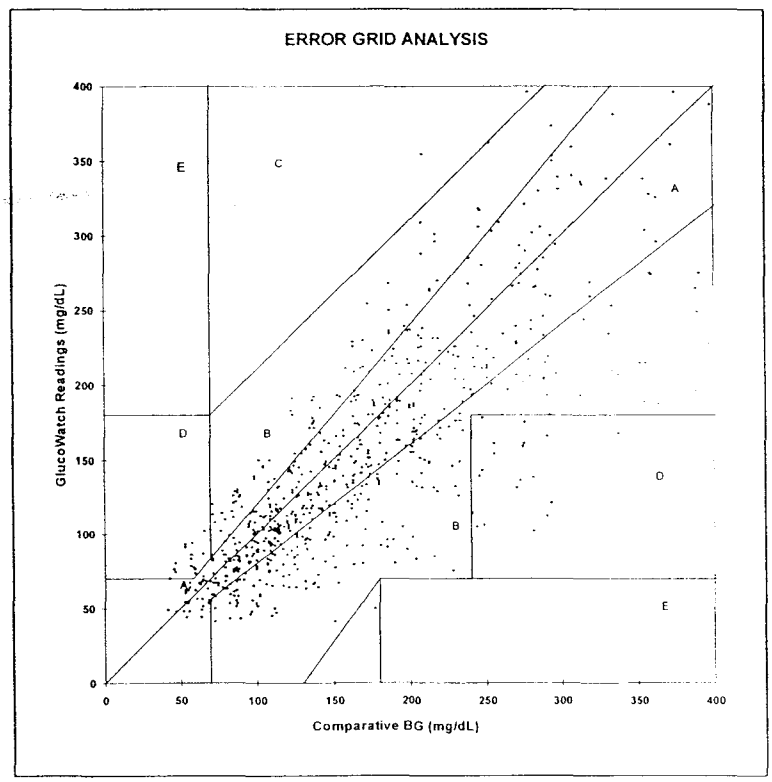
Regression analysis was used to characterize the relationship (slope and intercept) between the Biographer readings (dependent variable) and the comparative BG measurements (independent variable). Deming linear regression was used to account for variability in the comparative measurements. Data are presented in Table 4.

Table 4. Paired Point Results

Performance Parameter	Result
Paired glucose measurements	732
Mean absolute difference	21%
Deming regression slope (95% confidence interval)	0.88 (0.84, 0.92)
Deming regression intercept (95% confidence interval)	3.2 mg/dL (-2.0, 8.0)
Root mean squared difference	33.3 mg/dL

Instances of substantial variability were observed in the difference between individual GlucoWatch G2 Biographer readings and the paired comparative BG measurements. This can be seen in the Clarke Error Grid plot presented in Figure 1

Figure 1. Clarke Error Grid plot of GlucoWatch G2 Biographer readings versus home BG measurements **(N = 732 Paired Points)**



Some of the variability in agreement is related to the differences in sample source, timing of readings, and accuracy of the comparative devices. However, analyses of studies performed in adults have indicated that performance of the Biographer can vary from use to use (i.e., day 1 versus day 2) and within an individual 13-hour monitoring period.

The amount of Biographer variability in this juvenile population was analyzed by looking at the percentage of Biographer readings falling within 20% and within 30% of the comparative BG measurement (or within 20 mg/dL in the low BG range). Results are shown in Table 5.

Table 5. Differences Between Biographer and Blood Glucose Analyzer Measurements

	Paired Points		
BG range (mg/dL)	**# of paired points**	**% within 20%[a]**	**% within 30%[a]**
Overall	732	60%	76%
40-80	83	73%	73%
81-120	179	61%	75%
121-240	350	57%	78%
>240	120	53%	73%

[a]For the low glucose range (40-80 mg/dL) the value shown is the percent within 20 mg/dL

The Clarke Error Grid was used to assess the clinical relevance of the differences between the Biographer readings and the comparative BG measurements. The Error Grid divides a correlation plot into the five zones shown in Table 6.

Table 6. Description of Clarke Error Grid

Zone	Description	
A	Clinically accurate, would lead to correct treatment decisions	≤ 20% difference versus comparative BG measurement[c]
B	Would lead to benign decisions or no treatment	> 20% difference versus comparative BG measurement
C	Would lead to overcorrection of normal glucose levels	
D	Would lead to failure to detect and treat high or low glucose levels	
E	Would lead to erroneous treatment decisions	

[c]Also includes all points where both measurements are in the hypoglycemic range (≤ 70 mg/dL)

Results in zones A and B are considered clinically acceptable while results in zones C, D, and E are potentially dangerous and therefore are clinically significant errors. The Error Grid zones are labeled on the error grid plot presented in Figure 1.

In the study, 95% of Biographer readings were within the clinically acceptable error grid zones (A+B). No readings were observed in the erroneous treatment zone (E).

To assess the clinical relevance of Biographer performance at high and low glucose levels, the Error Grid results were stratified by BG range. Table 7 shows the overall distribution of points by Error Grid zone along with stratified results by four BG ranges.

Table 7. Error Grid by Blood Glucose Range

BG range (mg/dL)	# of paired points	A+B	A	B	C	D	E
Overall	732	95%	59%	36%	0%	5%	0%
41-80	83	82%	66%	16%	0%	18%	0%
81-120	179	100%	61%	39%	0%	Not applicable	
121-240	350	99%	57%	42%	1%		0%
241 - 399	120	83%	53%	30%	1%	16%	0%

3. Device Safety

No serious adverse consequences were observed in this clinical study in a juvenile population.

Because the GlucoWatch Biographer may cause skin redness and/or itching after use, each subject's skin was assessed immediately after Biographer removal and at subsequent follow-up visits. Data from the post removal and 4 day post removal assessments are summarized in Table 8. Most subjects experienced no or mild skin irritation (erythema and edema) at the extraction and adhesive sites after use of the device. No strong edema or blisters were observed at any of the wear sites. One wear site exhibited strong erythema at an adhesive site immediately upon device removal. All irritation was completely resolved within 4 days at adhesive sites. At the 4 day follow up assessment of extraction sites, none of the sites exhibited edema, and 96% of extraction sites had no erythema. All skin irritation was completely resolved at the next follow-up visit at 15 days post removal.

Table 8. Summary of Observed Skin Irritation at Two Assessment Time Points

Assessment	Adhesive Sites		Extraction Sites	
	Post removal (n=96)	**4-days Post Removal** (n=95)	**Post removal** (n=96)	**4-days Post Removal** (n=95)
Erythema				
No visible reaction	51%	100%	34%	96%
Mild erythema	48%	0	64%	4%
Moderate erythema	0	0	2	0
Strong erythema	1%	0	0	0
Intense erythema	0	0	0	0
Edema				
None	89%	100%	76%	100%
Barely visible	12%	0	24%	0
Light edema	0	0	0	0
Strong edema	0	0	0	0
Intense edema	0	0	0	0

3. Device failures and replacements

During the course of this study, 97 Biographers were used. One Biographer failed immediately after application, was removed, and replaced with another device. Three additional Biographers shut off early due to a low power condition, although they collected data and were included in the safety and efficacy Biographer populations described in this summary. These four failures were investigated as part of the Cygnus Corrective and Preventive Action (CAPA) program.

Root causes for the failures were determined. The device with the immediate failure was determined to be a result of a faulty device component. The low power problem has since been corrected through a device software revision. This revision was the subject of Supplement 9, approved in November, 2001.

X. CONCLUSIONS DRAWN FROM STUDIES

A. Safety Conclusions

No serious adverse health consequences were observed in the clinical study.

Most subjects experienced no or mild skin irritation (erythema and edema) at the extraction and adhesive sites after use of the device. Erythema classified as strong or intense was seen in 1% of the extraction sites and none of the adhesive sites. No strong edema or blisters were observed at the extraction or adhesive sites. The irritation was temporary and resolved within a few days.

These results were similar to results observed in earlier studies in adults (refer to the SSED for the approved PMA (P990026) for a summary of skin irritation data).

The proposed labeling includes a precaution statement directing users to apply the device to healthy skin and not to apply the device to any site at which irritation remains from previous use. Patients with suspected allergies to medical adhesives are directed to consult their health care professional before using the Biographer. The labeling also includes recommendations for managing skin irritation and directions to consult a health care professional if irritation does not begin to improve after 1 week.

B. Effectiveness Conclusions from the Preclinical Laboratory Studies

Refer to the SSED for the approved PMA (P990026) for the conclusions from the pre-clinical studies.

C. Effectiveness Conclusions from the Clinical Study

Clinical data collected through this study in juveniles shows device performance similar to that observed in adults (see SSED for PMA P990026).

The central assessment of the accuracy of the Biographer was based on the estimated bias (defined as the difference from y = x line to the Deming linear regression line) at five medical decision levels of glucose (50, 80, 100, 150, and 200 mg/dL). The 99% confidence intervals around the bias for all five medical decision levels were within ± 15mg/dL (%) thresholds, showing that bias estimates were significantly smaller than those thresholds.

The hyperglycemia and hypoglycemia alert functions of the Biographer provided useful clinical information. User selection of the low and high glucose alert levels is the key factor determining performance of the alert functions. A balance exists between sensitivity and the frequency of alerts to which the user must respond. The specifics of the alert situation provide useful information for deciding how to respond to an alert. For example, the lower the Biographer reading, the greater the probability that the subject was actually hypoglycemic based on the comparative result. Using conservatively chosen thresholds, the GlucoWatch G2Biographer detected a high percentage of hypo- and hyperglycemic events. The proposed labeling has been designed to advise both professionals and patients of the issues to consider when selecting the alert levels.

In this clinical study in juveniles, the slope of the Deming linear regression between the Biographer and the comparative measure was 0.88 while Deming intercept was 3.2 mg/dL with root mean squared difference = 33.3 mg/dL. Instances of substantial variability were observed between Biographer readings and their paired blood glucose measurements. For this reason, the labeling emphasizes the need to use the Biographer with finger-stick blood testing results.

Clinical utility of the Biographer readings was also demonstrated with analyses based on the Clarke Error Grid. In this study, 95% of the Biographer results were in the clinically acceptable zones (A + B), and no results were in the erroneous treatment zone (E zone)

XI. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Chemistry and Toxicology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the supplement substantially duplicates information previously reviewed by this panel.

XII. CDRH DECISION

It was determined that, based on the data submitted in the PMA supplement, the device has been shown to be safe and effective for the indications specified in the labeling. An approval letter was issued on AUG 26 2002

XIII. APPROVAL SPECIFICATION

Instructions for Use: See labeling.

Conditions of Approval: CDRH approval of this PMA supplement is subject to full compliance with the conditions described in the approval order.