SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name:	Automatic Glucose Biographer
Device trade name:	GlucoWatch® Automatic Glucose Biographer
Applicant's name and address:	Cygnus, Inc. 400 Penobscot Drive Redwood City, CA 94063
PMA number:	P990026
Date of Panel recommendation:	December 6, 1999
Date of notice of approval to the applicant:	March 22, 2001

II. INDICATIONS FOR USE

- The GlucoWatch Biographer is a glucose monitoring device indicated for detecting trends and tracking patterns in glucose levels in adults (age 18 and older) with diabetes. This device is intended for use by patients at home and in health care facilities.
- The GlucoWatch 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® Automatic Glucose 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 three glucose measurements per hour over a 12 hour measurement period, giving up to 36 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 3 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 12 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.

8

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 12-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 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 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 GlucoWatch 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.

- 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. Also, do not place the Biographer on a scrape, cut, sunburn, or razor burn. Skin irritation may be worse than normal. Instead, use a different site on your arm.

- 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 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 not been marketed in the United States. A similar device has been marketed in the United Kingdom (UK) since October, 2000.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No serious adverse consequences were observed in the clinical study. The use of the GlucoWatch Biographer may cause skin redness and/or itching after use. Symptoms should disappear within a week.

People with sensitive skin may experience more intense, but still temporary, redness or itching.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

A. Bench Testing

Linearity

Four GlucoWatch AutoSensors from each of three lots were tested for linearity. The test included five levels of -glucose aqueous control solutions to mimic blood glucose concentrations ranging from 25 mg/dL to 600 mg/dL. Four AutoSensors were tested at concentrations of 25 mg/dL, 50 mg/dL, 200 mg/dL, 400 mg/dL, and 600 mg/dL. Measurements were taken at selected cycles. The test was completed for each of three lots of AutoSensors. The AutoSensor response was plotted vs. the blood glucose equivalent concentration for each concentration level for each AutoSensor. All correlation coefficients were $\geq$ 0.999. These results demonstrate that an individual AutoSensor has a high degree of linearity.

Linearity regression analysis was performed in accordance with recommendations in NCCLS Document EP6-P, Vol. 6 No. 18, to produce a single linear regression plot per lot. The correlation coefficients were $\geq$ 0.991. These results demonstrate that the variation in performance between individual AutoSensors can have a small effect on the results for analysis of lots. However, since each individual AutoSensor is calibrated before use, this variation will not affect the degree of linearity experienced by a user.

Precision

Precision was tested in accordance with NCCLS Document EP5-T2, Vol. 12 No. 4. Three concentrations of glucose aqueous control solutions: low, 40 mg/dL; normal, 100 mg/dL; and high 400 mg/dL were used. Three AutoSensors were tested at each of the three concentrations for twelve hours per day on each of 10 days. This testing was repeated three times for each AutoSensor. The Biographers were programmed to run in the same manner as a patient system.

To analyze within-run precision, mean glucose, standard deviation (SD) and percentage coefficient of variance (%CV), were calculated for each concentration level for each AutoSensor using the 72 individual data points collected over the twelve hour period. Data analysis was conducted for each of the three glucose concentration levels and each of the three AutoSensor lots. For total precision, the mean glucose, SD and %CV results were calculated at each concentration level using all AutoSensors on all days tested. Data analysis was performed for the three different glucose concentration levels and AutoSensor lots.

Results for within-run precision indicate that %CV for each AutoSensor at each concentration level and each lot fall within a range of 0-11. The average %CV for each lot, as well as the overall %CV for all lots, are less than 4.

Results for total precision for all lots and all concentrations fall within the range of 4-8%CV. The data indicate that the GlucoWatch AutoSensor demonstrates a high degree of precision.

AutoSensor - QC Test

The QC Test allows the user to measure the AutoSensor response to a known concentration of glucose. After 20 minutes of conditioning, the AutoSensor was exposed to a 100 μM glucose solution. The AutoSensor then began to run a series of cycles. Measurements were taken at selected timepoints. These measurements were processed to obtain the "QC Reading".

To demonstrate whether the QC Test reading is an indicator of AutoSensor performance, the AutoSensor was maintained at 65°C for 24 hours. The QC reading decreased from 2.2 to 0.4, indicating loss of functional performance of the AutoSensor. As the protein content of the hydrogel contained in the AutoSensor degrades, the QC response decreases. These data show that the QC test correctly indicates the functional performance of the AutoSensor.

In addition, six lots of AutoSensors were tested to determine lot-to-lot variability by comparing the average QC test readings for each lot. All lots met specifications.

B. Chemistry

Glucose Oxidase

Glucose oxidase in the AutoSensor is incorporated in a cross-linked polyethylene oxide (PEO) gel. This hydrogel serves to provide electrode-skin contact, collection of extracted glucose and conversion of this glucose to hydrogen peroxide. Upon iontophoretic extraction of glucose, the glucose oxidase enzyme (GOx) converts glucose to hydrogen peroxide, which is detected at the Platinum/Carbon electrode of the sensor.

Glucose oxidase is fermented in Aspergillus niger cultures, then removed, purified, concentrated, formulated with stabilizing salts, and lyophilized to the final product.

During validation studies and through stability studies, GOx specific protein content and enzyme activity have been studied. These studies demonstrate that the specific protein content and its activity correlate well and provide a consistent ratio of the two measurements.

Interference Studies

The GlucoWatch Automatic Glucose Biographer system performs two separate functions in the monitoring process: glucose collection and glucose measurement. For a compound to affect the glucose signal it must both be extracted through the skin and interfere with the glucose biosensor function.

The GlucoWatch system design incorporates features to reduce the possibility of interference: it measures glucose at only the iontophoretic cathode, thus eliminating the possibility of interference by anionic species that are collected at the iontophoretic anode; the iontophoretic process involves human skin, which performs a filtering function; the use of hydrogel excludes highly insoluble (lipophilic) compounds from extraction; the sensor operates at a potential of 0.42V, which prevents compounds such as tyrosine from oxidizing to produce sensor signal.

In human subjects, ionotophoretic and passive samples were collected in a buffer solution reservoir on the skin's surface. The contents of the reservoir were removed and replenished with fresh buffer each hour, for five consecutive hours. The samples were then analyzed using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. A similar study was performed in which samples were taken every twenty minutes. The data show that compounds with pKa < 4.2 are sufficiently negatively charged to be collected only at the iontophoretic anode, and do not interfere with the glucose measurement. In a third study, iontophoretic skin extract from human subjects was analyzed using HPLC in conjunction with mass spectrometry. The results show no compounds with molecular weight greater than 400 daltons were detected.

Endogenous and exogenous compounds were selected for consideration as potential interfering species following NCCLS guideline EP7-P as well as the scientific literature on electrochemical blood glucose monitors. Forty-six compounds were considered, and twenty-six compounds were tested. The test methods were developed following the guidelines in NCCLS document EP7-P, with modification to accommodate the unique Biographer sample collection method. The modified method entails pipetting a known amount of glucose, both with and without the added candidate interfering substance, onto individual AutoSensors. Six replicates were performed of both the control glucose solution, and the glucose solution containing the interfering substance. An individual biosensor was used for each replicate.

Initial testing was performed at the test levels recommended by NCCLS EP-7P. Further tests were performed at concentrations which take into account the dilution factor caused by the transdermal extraction. Several compounds showed a potential to produce error on the glucose signal. It was determined that these compounds are surfactants, which can increase the sensor's sensitivity to glucose. Since this effect will equilibrate during the three-hour warm-up period of the biographer, these compounds will not affect the accuracy of any of the glucose values reported to the user.

Three compounds - acetaminophen, dopamine and tolazamide - were shown to induce significant error in the biosensor measurement of glucose at the concentrations tested. Dopamine and tolazamide are unlikely to be present during Biographer use. A limitation statement regarding concomitant use of these compounds is included in the proposed labeling. Because acetaminophen is a commonly used drug, the effect of this drug on device accuracy was investigated in a separate clinical study, more fully described in Section IX:

Summary of Clinical Studies. The results of the study suggest that acetaminophen is unlikely to cause any clinically significant effects on device performance.

C. Electrical Safety: Medical Electrical Equipment

The GlucoWatch Automatic Glucose Biographer was tested according to Standard IEC 60601-1:1998 + A1: 1991 + A2:1995 Medical Electric Equipment – Part 1; General Requirements for Safety. Passing results were obtained. The GlucoWatch Automatic GlucoseBiographer was tested according to Standard IEC 60601-1-4:96 Medical Electric Equipment – Part 1; General Requirements for Safety, 4. Collateral Standard; Programmable Electrical Medical System. Passing results were obtained.

D. Battery Testing

Nickel metal hydride

Nickel metal hydride batteries were tested at the three power levels used in the GlucoWatch Automatic Glucose Biographer. Testing was completed using the normal operational sequence of the biographer. Mean operating time exceeded requirements.

Lithium

Six GlucoWatch Automatic Glucose Biographers were used to test twenty-four lithium batteries. The batteries were fully discharged, and then twelve of the lithium batteries were charged for twenty-four (24) hours with AAA batteries, and twelve lithium batteries were charged for forty-eight (48) hours with AAA batteries. Operating life testing was done on each battery. All batteries exceeded requirements of the test.

E. Environmental Characteristics

Electromagnetic Compatibility

Testing of the GlucoWatch Automatic Glucose Biographer was completed pursuant to IEC 60601-1-2 standard and involved three separate tests; susceptibility to electro-static discharge (ESD), susceptibility to radio frequency (RF) noise and electromagnetic radiation from the Biographer. The Biographer was also tested for susceptibility to interference from cellular phones.

Three Biographers were tested. The software sequence used in the Biographer preconditioned the sensor for twenty minutes and subsequent readings were taken every ten seconds for three hours. Results demonstrate that the performance of the Biographer is not affected by interference from ESD and RF, and cell phones, and that no detectable electromagnetic radiation was emitted. The Biographer meets the requirements concerning electromagnetic compatibility as defined in EN60601-1-2.

Mechanical Shock - Operating

Three GlucoWatch Automatic Glucose Biographers were tested according to ANSI/AAMI EC38 requirements for mechanical shock while operating: "a 75 mm drop on a hard surface on any edge, face, or corner shall not interrupt normal glucose monitoring." The Biographer was dropped on all four corners, both faces and all four edges. The test was conducted with

the self-test sequence running and the self-test sensor attached. Results indicate that all three Biographers met the requirements of ANSI/AAMI EC38.

Mechanical Shock - Non-Operating

Three GlucoWatch Automatic Glucose Biographers were tested according to the requirements of ANSI/AAMI EC38. All Biographers passed the test.

Vibration

Two types of vibration testing were performed on the GlucoWatch Automatic Glucose Biographer: operational mode and non-operational mode. Three Biographers were tested. Each Biographer was put in a serial interface adapter (SIA) and then mounted to a fixture for the operational mode. Then, each Biographer was mounted directly to the fixture for the operational mode. In non-operational mode, the Biographers were tested according to the following criteria: 2.66 grms, from 5 to 500 Hz, 10 minutes each axis, when applied with the prescribed spectral density profile, shall cause no damage. The spectral density profile is Constant Applied Power Spectral Density Profile at 0.015 g^2/Hz from 5 Hz to 350 Hz, falling at -3 dB/octave to 0.015 g^2/Hz @ 500 Hz. In operational mode, the Biographers were tested according to the criteria: 0.3 grms, from 5 to 500 Hz, 10 minutes each axis when applied with the prescribed spectral density profile – 0.0020 g^2/Hz from 5 Hz to 350 Hz falling to 0.00014 g^2/Hz at 500 Hz.

Results indicate that the Biographers were functional for all three units during and after the operational test. They were also functional after the non-operational test.

Temperature/Humidity

Six GlucoWatch Automatic Glucose Biographers were tested according to the requirements of MIL-T-28800E and Cygnus Document 905-0387-00. These were tested at twelve checkpoints using these requirements over a ten-day period. Results indicate the six Biographers passed all checkpoints.

Altitude/Pressure

Two GlucoWatch Automatic Glucose Biographers were tested for performance in an altitude chamber simulating conditions at 10,000 ft and 19,000 ft above sea level. The biographers and their components passed the tests.

F. Reliability/Durability

Battery Springs

The fatigue test assumes a battery will be inserted and retracted (cycled) 3000 times. Five springs plated with electroless nickel were tested and passed the test. The battery springs were also tested, as part of the assembled test articles in the nonoperating mechanical shock drop test. During those tests, the battery springs must be able to retain the battery in place. The battery springs passed the tests.

IP Quality - Drip Proof

Three GlucoWatch Automatic Glucose Biographers were tested according to requirements of IEC 529 code IPX2. The test method was modified to use 200 mL of water sprayed on the test units, rather than 35 mL of water dripped on the units. After 24 hours of exposure, the Biographers passed subsequent testing.

Biographer Speaker

Four Biographers were subjected to 100 hours of continuous full amplitude speaker operation. The sound level output (in dB) was measured for each Biographer, and recorded at three distances. After the test, the sound level output was measured for each test article.

The Piezo-Bender Speaker will survive 10,000 hours driven at worst case levels of 30 Vpp at typical Biographer duty factors. The speakers suffered no adverse or irreversible effects when subjected to the stress tests.

G. Stress Summary

Stress testing was performed to verify that the Biographer performed as expected during Preconditioning, Measurement and Post-measurement cycles. Functions assessed during these cycles include 1) correct measurements occurring at proper times, 2) Ionotophoresis and Biosense stimuli match the predicted models, and 3) glucose readings taken under stress are within the tolerances specified and correlate to nonstress conditions. Eight tests were completed.

The GlucoWatch Automatic Glucose Biographer passed the stress tests. Its performance is not specifically affected by software stress conditions.

H. MRI Compatibility

Proposed labeling includes a limitation statement, that Biographer readings may be affected by procedures when there are high electro-magnetic fields.

I. Firmware/Software

The GlucoWatch Automatic Glucose Biographer is controlled by firmware, which controls all low-level functions of the device, and sequences, which are written in a command language and control all functions associated with glucose monitoring. The level of concern for the software system is considered moderate, according to the rationale described in the FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. Validation of the sequences was performed in four stages. The firmware was verified with both Module Testing and Integration Testing. Proper execution of all commands was verified.

J. Hazard Analysis/Risk Assessment

Fault Tree Analysis Program

A Fault Tree Analysis of potential system safety risks was performed for the GlucoWatch Automatic Glucose Biographer. The results of this analysis were used in the design of the Biographer.

Failure Mode & Effects Analysis

A Failure Mode & Effects Analysis (FMEA) was completed for the GlucoWatch Automatic Glucose Biographer. All failure modes associated with the use of the Biographer, the cause of each failure mode, the effect that each failure mode has on the performance of the Biographer, and the method used to detect each failure mode were identified in the FMEA. The FMEA is sufficient and the results were used in the design of the Biographer.

Safety Requirements Tracking Matrix

Safety requirements were identified in the fault tree analysis performed on the GlucoWatch Automatic Glucose Biographer system. These requirements are subject to review when changes are proposed that could impact product safety.

K. Biological Testing

Toxicology: Cytology

Tests required were determined according to the requirements of ISO 10993 Biological evaluation of medical devices. Tests were chosen based on the fact that the GlucoWatch Automatic Glucose Biographer is worn on intact skin surfaces for less than 24 hours. Biocompatibility tests include: cytotoxicity (mouse fibroblast cell culture), intracutaneous reactivity (rabbit), and sensitivity (guinea pig, maximization).

Cytotoxicity testing was conducted using methods that comply with ISO 10993-5 IS010993-12 and USP 23. Results from cytotoxicity testing indicate that Biographer and AutoSensor components not containing gel present a safe profile for patient skin during the wearing period. The components containing the hydrogel, which included glucose oxidase, were identified as cytotoxic. When the hydrogel was tested without glucose oxidase, the hydrogel itself was determined to present acceptable toxicity. These cytotoxicity results were not predictive of the results obtained in the animal model testing.

The enzymatic action of glucose oxidase, and not the molecule itself, is proposed as the toxicity mechanism for the effects noted in the cytotoxicity testing. This mechanism is described in the literature. The glucose present in the culture medium surrounding the mouse fibroblast cells is converted to gluconic acid and hydrogen peroxide. Hydrogen peroxide is the toxin that kills the cells. In addition, removal of glucose from the medium leaves the cells without adequate nutrition, potentially resulting in cell death. The lack of toxicity observed in living skin may be due to the catalase in living skin, which converts hydrogen peroxide to water and oxygen, thereby detoxifying the material, so that it does not produce the type of response predicted in the cytotoxicity testing. The T lymphocyte is one type of cell that may play a role in this detoxifying process. T lymphocytes were not present in the cultures employed in the agar diffusion and elution cytotoxicity tests. In addition, the blood perfusion of living dermis would minimize localized build-up of small molecular toxins, such as hydrogen peroxide, since these are highly permeable.

The animal testing results were predictive of the clinical results. In the clinical irritation study, only mild to moderate irritation was observed following 15 hours of wear. The active Biographer was also tested for sensitization potential in a study design, which included AutoSensors that employed either a gel containing glucose oxidase or a blank gel not containing glucose oxidase. No increase in irritation levels was determined to be due to the glucose oxidase. The Biographer demonstrated no sensitization potential. The irritation

observed was due in large part to the presence of electric current and potential for mechanical friction. No cytotoxicity was evident. The irritation was temporary, and resolved upon removal of the device. Since the application site is to be rotated, any irritation should be resolved readily in actual use situations.

Biocompatibility

Intracutaneous Reactivity - The intracutaneous reactivity study tested extracts of Biographer components, which would contact patient skin during the 15-hour wearing period. Test methods were chosen according to ISO 10993-10 and ISO 10993-12 and LISP 23. Test materials were injected within the skin of New Zealand white rabbits. This method ensures that the test material contacts living skin cells. The extracts did not show significantly greater biological reaction than the control article and were considered negligible irritants.

Skin Sensitization - The skin sensitization study method was the Skin Sensitization Kligman Maximization test. Extracts of Biographer components, which would contact patient skin during the 15-hour wearing period, were tested. Test methods were chosen according to ISO 10993-10, ISO 10993-12, and USP 23. The test materials were injected into the skin and also applied topically to the skin of guinea pigs. The test methodologies ensure that the test materials) contact living skin cells. As defined by the scoring system of Kligman, the extracts elicited a Grade I reaction, which is not considered significant according to Magnusson and Kligman.

The results of animal testing for skin sensitization and irritation were predictive of the clinical results. The active Biographer was tested for sensitization potential in a study design that included AutoSensors that employed either a gel containing glucose oxidase or a blank gel not containing glucose oxidase. No increase in irritation levels was determined to be due to the glucose oxidase. The Biographer demonstrated no sensitization potential. The irritation observed was due in large part to the presence of low-level electric current and potential for mechanical friction. No cytotoxicity was evident. The irritation was temporary, and resolved upon removal of the device.

L. Reuse

The GlucoWatch Automatic Glucose Biographer is designed to have an expected useful life of at least four years when worn daily and stored and cared for according to the labeling.

M. Shelf Life

AutoSensor Stability

Twelve lots of AutoSensors have been studied under controlled conditions (5°C and 25°C/60%RH). All results for all lots are well within the set Stability Specifications.

AutoSensor at Extreme Temperature

Ten AutoSensors were tested in a cycle that included cycles of extreme temperature changes (4°C, 37°C and 45°C). All AutoSensors exhibited performance characteristics that exceeded requirements. AutoSensors were tested under freeze-thaw conditions. All the AutoSensors exhibited performance characteristics that exceeded requirements.

QC Test Solution (glucose)

Three lots of QC Test Solution were tested under a protocol that had two sets of test conditions: 25°C/60%RH and 40°C/75%RH. The first set of test conditions will be tested for 24 months. The accelerated stability test has a 6-month time period. All results for all lots show acceptable stability for up to 6 months of study time. All results are well within the set specifications. The studies will continue to completion.

IX. SUMMARY OF CLINICAL STUDIES

A series of controlled clinical studies were conducted to evaluate the performance of the GlucoWatch Biographer. In all cases, 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 studies. In order to evaluate the data from these studies, 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.

Each study was designed to evaluate the performance of the device in a particular setting, or to assess one of several features of the device. 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 20 minutes. For the clinical studies, only one or two fingerstick meter values (depending on the study) were 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 23 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 20 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 or two blood measurements were made each hour, only two-thirds 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, especially in home use situations, 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. Except for some analyses conducted to evaluate the subset of subjects who calibrated the device at very high glucose levels, not a single data point from any of the clinical studies was excluded as being an outlier from any of the primary performance analyses.

- The measurement techniques of the GlucoWatch Biographer and traditional blood glucose meters are inherently different. The Biographer design prevents the type of comparison that can be obtained from using a single finger-puncture capillary blood sample to produce a reading in two or more traditional meters, i.e., a "split sample". Because there is not an exact correlation of the two samples being measured, the comparative accuracy of the Biographer is underestimated.

A. Study Design, Patient Assessment, Demographics

This summary is based upon the results of nine pivotal clinical studies. Effectiveness of the GlucoWatch Biographer was assessed in seven studies. Four of the effectiveness studies (Primary Studies) were of similar design and tested the same hypothesis in different use situations and with a series of different calibrating and comparative glucose monitoring systems. The other three effectiveness studies were designed to investigate specific features or aspects of Biographer performance. The safety analyses are based on the seven effectiveness studies along with two additional studies specifically designed to investigate skin irritation and sensitization. Study designs, objectives, and demographic data are summarized in Table 1 (the four similar primary effectiveness studies), Table 2 (the three additional effectiveness studies) and Table 3 (the additional safety studies).

For the effectiveness studies, subjects were over 18 years of age with either type 1 or type 2 diabetes requiring treatment with insulin. Subjects also provided written informed consent and had a clinically acceptable medical history as determined by the investigator. Subjects were excluded if they required electrically sensitive support systems (e.g., pacemakers), had any significant wounds or injuries at the Biographer wear site, had taken acetaminophen within 72 hours of study initiation or had a hematocrit value outside the range specified in each of the comparative meter's labeling. Subjects were also excluded if they were unable to forego application of topical products to the wear sites during the study or unable to refrain from smoking during studies requiring a controlled clinical environment.

Table 1. Design and Objectives for the Four Primary Effectiveness Studies

	Study 1	Study 2	Study 3	Study4
Study Name	Accuracy	Home Simulated	Home Environment	Lab Method Comparison
Primary Objective	Determine accuracy in controlled clinical setting	Determine accuracy in home simulated setting	Determine accuracy in actual home use	Determine accuracy in home simulated setting
Hypothesis Tested (Basic Design)	Predicted bias (defined as difference from the Deming linear regression) at five medical decision levels of glucose. Null hypothesis was that bias 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	HemoCue analyzer	One Touch Profile meter	YSI analyzer
Calibrating Device	HemoCue analyzer (supplemental analysis with four home meters)	One Touch Profile meter	One Touch Profile meter	YSI analyzer
Duration of Use	1 day (15 hours)	2 days & 1 night	5 days	1 day
Number of Sites	6	6	6	1
Number of Subjects				
Safety population	231	134	124	31
Efficacy population	221	120	111	28
Demographics				
Age (years)				
Mean	48.2	48.4	46.5	50.0
SD	15.0	12.1	11.7	16.2
Race (%)				
African Am.	10.4	11.9	8.9	9.7
Caucasian	71.9	85.8	79.8	54.8
Hispanic	15.6	0.7	7.3	35.5
Other	2.1	1.6	4.0	0.0
Gender (%)				
Female	51.9	64.9	62.9	48.4
Male	48.1	35.1	37.1	51.6
Diabetes Type (%)				
Type 1	64.5	54.5	59.7	48.4
Type 2	35.5	45.5	40.3	51.6

21

Table 2. Design and Objectives for the Three Additional Effectiveness Studies

	Study 5	Study 6	Study 7
Study Name	**Home Use Precision**	**Extended Wear**	**Acetaminophen**
Primary Objective	Determine precision in actual home use	Determine whether performance is similar in short term and extended wear in a home setting	Evaluate effect of acetaminophen as a potential interfering substance
Basic Design	Subjects wore two Biographers simultaneously. Day 1 was in a clinic setting. Day 2 and 3 were at home or work.	Subjects wore the Biographer daily for six weeks. Four in-clinic accuracy studies were conducted on days 1, 15, 30 and 43.	Day 1: subjects took no acetaminophen. On Day 2: Group 1 took acetaminophen before calibration and Group 2 took acetaminophen after calibration.
Hypothesis Tested	No formal hypothesis test	Analysis of variance for seven performance measures across four clinic visits over 6 weeks	Two one-sided Wilcoxon tests of the difference in mean error with and without acetaminophen
Comparative Device	Not applicable	HemoCue analyzer	HemoCue analyzer
Calibrating Device	One Touch Profile meter	HemoCue analyzer	HemoCue analyzer
Duration of Use	3 days	43 days	2 days
Number of Sites	1	1	1
Number of Subjects			
Safety population	24	15	18
Efficacy population	22	15	18
Demographics			
Age (years)			
Mean	50.8	33.1	30.4
SD	14.7	8.9	5.6
Race (%)			
African Am.	4.2	0.0	0.0
Caucasian	95.8	100	100.0
Hispanic	0.0	0.0	0.0
Other	0.0	0.0	0.0
Gender (%)			
Female	41.7	53.3	50.0
Male	58.3	46.7	50.0
Diabetes Type (%)			
Type 1	66.7	100	100.0
Type 2	33.3	0.0	0.0

22

Table 3. Design and Objectives for the Additional Safety Studies

	Study 8	Study 9
Study Name and Protocol Number	**Acute Irritation**	**Contact Sensitization**
Primary Objective	Evaluate potential to cause skin irritation	Evaluate induction of contact sensitization by repetitive applications
Basic Design	Multiple follow-up visits after one 15 hour wear period during which four Biographers were worn by each subject	9 repetitive applications for 14 hours over 3 weeks followed two weeks later by an 8 hour challenge application
Number of Sites	6	1
Number of Subjects	103	99
Demographics		
Age (Range: Pop.%)		
	18 – 44: 31%	18 - 49: 40%
	45 - 79: 69%	50 – 80: 60%
Race (%)		
African Am.	5.8	10.0
Caucasian	93.2	81.0
Other	1.0	9.0
Gender (%)		
Female	68.0	70.7
Male	32.0	29.3
Diabetes (%)		
Y	49.5 (Type 1 & Type 2)	40.4 (Type 1 & Type 2)
N	50.5	59.6

B. Data Analysis and Results

Four studies of similar design were conducted to assess the effectiveness of the GlucoWatch Biographer in different use environments. Biographer readings were compared to blood glucose (BG) tests performed once or twice per hour. Subjects in these studies were 18 years of age or older with either type 1 or type 2 diabetes requiring treatment with insulin. The design of these studies is summarized Table 4:

Table 4. Design of the Four Primary Effectiveness Studies

	Study 1	Study 2	Study 3	Study 4
Environment	Clinic	Home Simulated	Home Use	Home Simulated
Calibrating Device	HemoCue® photometer[a]	One Touch® Profile™ meter	One Touch® Profile™ meter	YSI analyzer[b]
Comparative Device	HemoCue® photometer[a]	HemoCue® photometer[a]	One Touch® Profile™ meter	YSI analyzer[b]
Duration of Use	1 day (15 hrs)	2 days and 1 night[c]	5 days	1 day (15 hrs)
Subjects	221	120	111	28

[a]A point-of-care system that provides lab-quality results

[b]A standard laboratory method for measuring glucose levels

[c]Comparative BG measurements were only made during the daytime periods

For the four primary clinical studies, the central assessment of the accuracy of the Biographer was based on the predicted bias (defined as the difference from the Deming linear regression) at five medical decision levels of glucose (50, 80, 100, 150, and 200 mg/dL). In all four studies the null hypothesis (bias >15 mg/dL at 50 and 80 mg/dL or bias >15% at 100, 150 and 200 mg/dL) was rejected indicating that, on average, the Biographer did not give readings that were systematically low or high relative to the comparative methods. This conclusion was consistent regardless of use situation (clinical settings, simulated home use, or actual home use), calibrating method (HemoCue® analyzer, YSI analyzer, or One Touch® Profile™ meter), or comparative method (the same three systems).

Detection of Trends and Patterns in Glucose Levels

The GlucoWatch Biographer readings closely matched the direction and speed of changes reflected in the blood glucose data. The median correlation coefficient was approximately 0.90 in each of the four studies.

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 from Study 3 were analyzed using a definition of hypoglycemia as a BG measurement of 70 mg/dL or below on the home BG meter. At a Low Glucose Alert level of 100 mg/dL, 75% (120/160) of the events of hypoglycemia were detected by the Biographer (see table below). In addition, the Biographer correctly identified the absence

of hypoglycemia on 90% (2599/2900) 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 5.

Table 5. Events of Hypoglycemia Detected by the Biographer

	BG ≤ 70 mg/dL	BG > 70 mg/dL
Biographer reading ≤ 100 mg/dL	120	301
Biographer reading > 100 mg/dL	40	2599
Total	160	2900

Based on patient logbooks from this study, BG monitoring twice per day would have detected 19% of hypoglycemic events; BG monitoring four times per day, 39%. Thus, use of the Biographer to supplement standard BG monitoring can improve detection of hypoglycemia.

The Biographer can also be used to improve detection of hyperglycemia. Post-prandial hyperglycemia was common in the home use environment of Study 3. Out of 974 evaluable post-meal periods, 456 (47%) had a post-prandial BG level of greater than 200 mg/dL and 238 (24%) had a post-prandial BG level of greater than 250 mg/dL. None of these hyperglycemic events would be detected with standard pre-meal BG testing alone.

To assess Biographer detection of hyperglycemia, Study 3 results were analyzed using a definition of BG ≥ 300 mg/dL. At a High Glucose Alert level of 240 mg/dL, 86% (132/154) of the events of hyperglycemia were detected by the Biographer (see table below). In addition, the Biographer correctly identified the absence of hyperglycemia on 86% (2491/2906) of the occasions when BG was less than 300 mg/dL. Data are presented in Table 6.

Table 6. Events of Hyperglycemia Detected by the Biographer

	BG ≥ 300 mg/dL	BG < 300 mg/dL
Biographer reading ≥ 240 mg/dL	132	415
Biographer reading < 240 mg/dL	22	2491
Total	154	2906

Agreement Between Individual Biographer Reading and Blood Glucose Test results

Different methods were 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. In addition, in the home use studies the comparative system was a home meter, which has greater variability than a standard laboratory analyzer. These differences in sample source, timing of reading and comparison systems all 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 each 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.

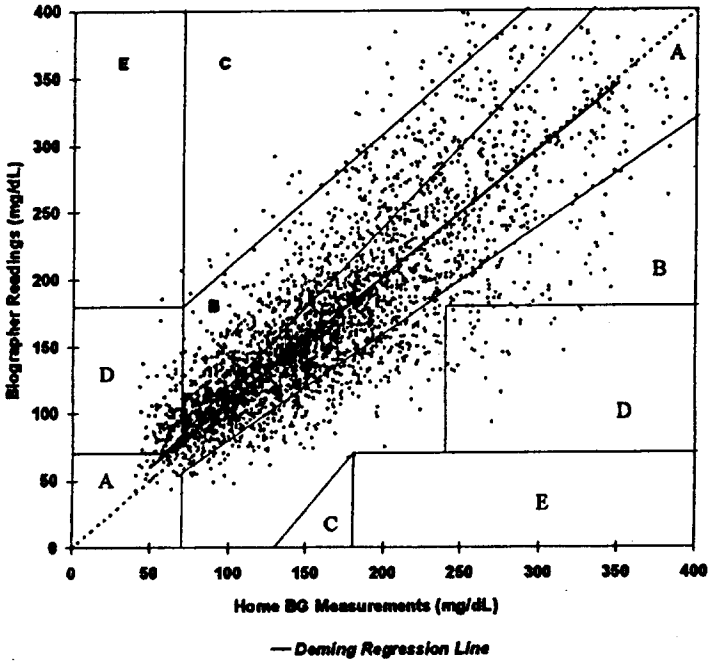
Table 7. Paired Point Results from the Four Primary Effectiveness Studies

	Study 1	Study 2	Study 3	Study 4
Environment	Clinic	Home Simulated	Home Use	Home Simulated
Paired Glucose Measurements	6909	3771	2996	416
Mean absolute Difference	19%	21%	21%	17%
Deming Regression Slope	0.93	1.00	0.95	0.94
(95% confidence interval)	(0.92, 0.95)	(0.97, 1.03)	(0.91, 0.99)	(0.88, 1.01)
Deming Regression Intercept	12 mg/dL	0 mg/dL	13 mg/dL	8 mg/dL
(95% confidence interval)	(9, 15)	(-5, 4)	(7, 18)	(-1, 17)

Substantial variability was observed in the difference between individual GlucoWatch Biographer readings and the paired comparative BG measurements. This can be seen in the correlation plot for Study 3 presented in Figure 1.

Figure 1. Correlation Plot of GlucoWatch Biographer Readings versus Home BG Measurements from Study 3

(N = 2996 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 have indicated that performance of the Biographer can vary from use to use (i.e., day 1 versus day 2) and within an individual 12 hour monitoring period.

The amount of variability 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 shown in Table 8 illustrate the differences seen when using a home meter for comparison (Study 3) versus a standard laboratory analyzer (Study 4).

Table 8. Differences Using a Home Meter vs. Standard Laboratory Analyzer

	Home Meter			Standard Laboratory Analyzer		
	Study 3			Study 4[b]		
BG range (mg/dL)	**# of paired points**	**% within 20%[a]**	**% within 30%[a]**	**# of paired points**	**% within 20%[a]**	**% within 30%[a]**
Overall	2996	61%	76%	420	71%	86%
40-80	261	45%	45%	42	67%	67%
81-120	598	59%	72%	93	71%	82%
121-240	1706	64%	82%	246	73%	89%
> 240	431	63%	79%	39	62%	95%

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

[b]For this analysis a home meter result was used for calibration and the YSI analyzer was used for comparative values

The Clarke Error Grid was used to assess the clinical relevance of the differences between the Biographer readings and the comparative BG measurements.[2] The Error Grid divides a correlation plot into the five zones shown in Table 9.

Table 9. Description of Clarke Error Grid

Zone	Description	
A	Clinically accurate, would lead to correct treatment decisions	≤ 20% difference versus comparative BG measurement *
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	

*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 clinically significant errors. The Error Grid zones are labeled on the correlation plot from Study 3, Figure 1.

In the 4 effectiveness studies, the percent of Biographer readings within the clinically acceptable zones (A and B) ranged from 94% to 98%. Less than one out of every 1,000 Biographer readings (8 out of a total of 14,092 paired readings) were 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. Tables 10 and 11 show the overall distribution of points by Error Grid zone for Studies 3 and 4 along with stratified results by four BG ranges.

Table 10. Study 3: Error Grid by Blood Glucose Range

BG range (mg/dL)	# of paired points	A+B	A	B	C	D	E
Overall	2996	94%	60%	34%	1%	4%	0.1%
40-80	261	63%	35%	28%	0.4%	36%	0.8%
81-120	598	99%	59%	41%	0.7%		
121-240	1706	98%	64%	35%	2%		0.1%
> 240	431	90%	63%	27%	2%	8%	0.0%

Table 11. Study 4: Error Grid by Blood Glucose Range

BG range (mg/dL)	# of paired points	A+B	A	B	C	D	E
Overall	420	98%	70%	28%	0.0%	2%	0.0%
40-80	42	81%	57%	24%	0.0%	19%	0.0%
81-120	93	100%	71%	29%	0.0%		
121-240	246	100%	73%	27%	0.0%		0.0%
> 240	39	97%	62%	36%	0.0%	3%	0.0%

In Study 3, 94% of the Biographer readings were in the clinically acceptable zones (A and B). Four percent (4%) of Biographer readings fell into zone D. Most of the zone D results occurred in the low range when the home meter BG was below 70 mg/dL and the Biographer reading was greater than 70 mg/dL. This type of low-range zone D error has also been seen with standard home BG meters.

In Study 4, when a more accurate laboratory analyzer (YSI) was used for comparison, 98% of Biographer readings were in zones A and B and 2% were in zone D. Again, most of the zone D results occurred in the low BG range.

Three Additional Effectiveness Studies and Two Safety Studies

Precision was estimated by comparing readings from 2 Biographers worn simultaneously at different skin sites by subjects (n = 21) over 3 days. The first day was in a home-simulated environment and the final 2 days were during actual home use. Table 12 shows the median within individual results from the home use period.

Table 12. Results From Study 5 (Precision Study)

Average Biographer reading (mg/dL)	# of individuals	# of paired points	Median standard deviation	Median (range) percent coefficient of variation
Overall	21	765	17 mg/dL	10% (3%, 19%)
40-80	14	59	6 mg/dL	9% (1%, 21%)
81-120	18	155	9 mg/dL	8% (3%, 16%)
121-240	21	472	18 mg/dL	10% (3%, 19%)
> 240	13	79	33 mg/dL	12% (2%, 24%)

The variability between paired Biographer readings increases as a function of glucose range. All covariances for each individual were < 25% both overall and within each glucose range. Note that this experimental method includes additional sources of variability compared to the standard precision study in which repeated measurements are made from a single sample of capillary blood.

Most subjects in the effectiveness and safety studies experienced mild to moderate 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 less than 2% of the extraction and adhesive sites. Strong edema was seen in less than 1% of the extraction and adhesive sites. The irritation was temporary and resolved within a few days. There was no indication of contact sensitization.

An extended wear study was conducted in which subjects (n = 15) wore the Biographer daily for 6 weeks. Four in-clinic accuracy studies were completed on days 1, 15, 30, and 43. No significant changes were observed in any accuracy measure or in skin irritation scores during the 6 week study period.

Another study was conducted to evaluate the effect of acetaminophen as a potential interfering substance on the accuracy of the Biographer readings. Based on study results, there is no clinically significant effect of acetaminophen on device performance.

Device failures and replacements

Over the course of these nine studies, there were a total of five devices returned. Data from these devices were not used in any of the analyses. In one study, thirty-eight devices initially failed to download data as expected. These devices were evaluated and repaired. The data were retrieved, verified and included in the analyses of the study.

X. CONCLUSIONS DRAWN FROM STUDIES

A. Safety Conclusions

Non-clinical laboratory studies have demonstrated safety of the device. A complete hazard analysis and risk assessment of the device have been completed. *In vivo* biocompatability studies in animals demonstrated the safety of all materials in contact with the skin during use of the device.

Across all nine pivotal clinical studies, there were no serious adverse health consequences.

Most subjects experienced mild to moderate 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 less than 2% of the extraction and adhesive sites. Strong edema was seen in less than 1% of the extraction and adhesive sites. Blisters, predominately in adhesive areas, occurred at less than 3% of the sites. The irritation was temporary and resolved within a few days. In the extended use study, there was no difference in irritation at wear sites analyzed on days 1, 15, 30 and 43. There was no indication of contact sensitization in a test model using an adaptation of the Draize patch test procedure.

The proposed labeling includes a caution statement directing users not to apply the device to any site at which irritation remains from previous use. The labeling also includes recommendations for managing skin irritation and directions to consult a health care professional if irritation does not resolve within 1 week.

B. Effectiveness Conclusions from the Preclinical Laboratory Studies

Bench top testing demonstrated a high degree of linearity and precision. Laboratory studies explored and discounted the potential for interference with the glucose readings due to varying levels of physiologic compounds or administration of most therapeutic drugs. Proposed labeling includes a limitation statement regarding use of the device in subjects undergoing therapy with dopamine or tolazamide, which have not been ruled out as potential interfering species.

Product testing has demonstrated compliance with relevant standards for electrical safety, environmental variability and potential interference, reliability, durability, and software design and validation. Proposed labeling includes a limitation statement regarding use of the device during magnetic resonance imaging and similar procedures.

C. Effectiveness Conclusions from the Clinical Studies

For the four primary clinical studies, the central assessment of the accuracy of the Biographer was based on the predicted bias (defined as the difference from the Deming linear regression) at five medical decision levels of glucose (50, 80, 100, 150, and 200 mg/dL). In all four studies the null hypothesis (bias >15 mg/dL at 50 and 80 mg/dL or bias >15% at 100, 150 and 200 mg/dL) was rejected indicating that, on average, the Biographer did not give readings that were systematically low or high relative to the comparative methods. This conclusion was consistent regardless of use situation, calibrating method or comparative method.

The hyperglycemia and hypoglycemia alert functions of the Biographer provided useful clinical information in all use situations. 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 Biographer detected a high percentage of hypo- and hyperglycemic events. The alert function was also shown to be effective at awakening subjects from sleep. The proposed labeling has been designed to advise both professionals and patients of the issues to consider when selecting the alert levels.

In all four studies, the slope of the Deming linear regression between the Biographer and the comparative measure was close to unity (0.93 to 1.00 for the Biographer compared to 0.85 to 1.04 for home meters). The Deming intercept was always close to zero (-0.1 to 12.6 mg/dL for the

Biographer compared to –3.3 to 36.8 mg/dL for home meters). Thus, the results indicate that, on average, the accuracy of the Biographer is similar to that of existing home blood glucose meters. However, 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 studies with the GlucoWatch biographer, approximately 95% of the Biographer results were in the clinically acceptable zones (A + B). Results in Zone E of the Clarke Error Grid occurred extremely rarely (only 10 out of 18,557 paired readings).

XI. PANEL RECOMMENDATION

A meeting of the Chemistry and Toxicology Devices Advisory Panel was held on December 6, 1999, to discuss this PMA. The Panel unanimously voted recommending approval of the PMA subject to the following conditions:

- Conduct a postmarket evaluation on the use of the device specifically in its ability to detect the frequency of both hypo- and hyperglycemic episodes.
- Conduct a postmarket study to evaluate the effects of skin irritation on device performance.

XII. CDRH DECISION

ODE determined that, based on the data submitted in the PMA, the device has been shown to be safe and effective for the indications specified in the labeling, pending the satisfactory resolution of outstanding GMP issues and a successful GMP inspection, and issued an approvable letter on May 8, 2000. A GMP inspection of the applicant's manufacturing site was re-conducted on January 9, 2001. The site passed inspection and it was determined that the firm has an acceptable GMP program. An approval letter was issued on March 22, 2001.

XIII. APPROVAL SPECIFICATION

Instructions for use: See labeling

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