SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Continuous Subcutaneous Glucose Monitoring System
Device Trade Name:	Continuous Glucose Monitoring System (CGMS)
Applicant's Name and Address:	MiniMed Inc. 12744 San Fernando Road Sylmar, California 91342
PMA Number:	P980022
Date of Panel Recommendation:	February 26, 1999
Date of Notice of Approval to Applicant:	June 15, 1999

II. INDICATIONS FOR USE

The Continuous Glucose Monitoring System (CGMS) is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace, blood glucose information obtained using standard home glucose monitoring devices. The information collected by the CGMS may be downloaded and displayed on a computer and reviewed by health care professionals. This information may allow identification of patterns of glucose level excursions above or below the desired range, facilitating therapy adjustments which may minimize these excursions.

- The system is intended for prescription use only,
- Will not allow readings to be made available directly to patients in real time,
- Provides readings that will be available for review by physicians only after the entire recording interval (suggested as 72 hours),
- Is currently intended for occasional rather than everyday use, is to be used only as a supplement to, and not a replacement for, standard invasive measurement,
- Is not intended to change patient management based on the numbers generated, but to guide future management of the patient based on response to trends noticed. That is, these trends or patterns may be used to suggest when to take fingerstick glucose measurements to better manage the patient.

III. DEVICE DESCRIPTION

A. Overview

The MiniMed Continuous Glucose Monitoring System (CGMS) is comprised of five principal components: (1) a monitor, (2) a sterile, disposable subcutaneous glucose sensor with an external electrical connector, (3) a connecting cable, (4) a Com-Station which allows data stored in the monitor to be downloaded to a personal computer, and (5) a test plug used to confirm the function of the sensor, cable and monitor. The system is designed to provide continuous measurement of glucose concentration in interstitial fluids over a range of 40 to 400 mg/dL. The information collected by the CGMS is intended to provide adjunctive data to physicians who are interested in monitoring the daily fluctuations in their subjects' glucose levels.

B. Description of Components

Glucose Monitor:

The glucose monitor, approximately the size of a pager, serves as a data collection unit which processes the signal received from the glucose sensor.

The glucose monitor is designed to provide power to the sensor, measure the sensor current, perform data smoothing and filtering, facilitate device calibration, provide storage of historical glucose data and transfer data to a personal computer via an infrared serial communication port.

The glucose sensor signal is acquired every 10 seconds. A smoothed average of acquired signals is saved in memory every 5 minutes.

The monitor is capable of storing glucose signals for up to 14 days. The glucose sensor signal acquisition occurs continuously once the CGM is turned on and initialized.

The display of the glucose monitor is a LCD utilizing a combination of fixed icons, seven-segment numeric characters and sixteen-segment alphanumeric characters. Backlighting can be activated with a single button push.

The user enters configuration, control, and calibration information via five membrane keypad buttons; SEL, ACT, ↑, ↓, and ON/OFF. Using a variety of combinations of information displayed on the LCD screen and the keystrokes made by the user, the CGM is configured to perform its built-in functions and indicate the status related to them. The screens and the keystrokes are organized according to a well-defined menu structure. Visual (alarm and alert displays) and audible (alert tones and tone sequences) indications are provided to alert the user of error conditions.

Glucose Sensor:

The Glucose Sensor consists of glucose sensing electrodes plated on a flexible substrate housed in a polyurethane tube; a rigid introducer needle; a base disk containing contact pads which act as electrical connectors; a seal which provides a water tight connection; a needle guard; and an adhesive patch.

The components are assembled and sealed in a pouch with sterilization and temperature indicators. The Glucose Sensor is a sterile disposable unit. The customer box includes an additional temperature indicator.

Cable:

The cable provides a continuous link between the glucose sensor and the glucose monitor. It consists of a grounded, coated copper cable; a male, four-pin connector plug to the monitor; and a female, three leaf spring connector to the glucose sensor.

Com-Station:

The Com-Station is a cradle-like unit that is form-fit for the monitor. The Com-Station converts infrared (IR) pulses from the monitor into RS-232 compatible electrical pulses that are sent through a serial port to the PC. A second RS-232 serial port allows the Com-Station to act as a pass through connection to allow the user to connect any serially accessed peripheral device to their PC without disconnecting the Com-Station. A compatible glucose meter may be connected to the PC utilizing the pass-through feature. The Com-Station allows retrieval and review of the patient's glucose monitor data.

A switch selects between IR communication and the second RS-232 connector. An AC adapter powers the unit. An illuminated ON/OFF switch indicates to the user when power is applied.

Windows 95 compatible PC Resident software (model 7310) is provided with the Com-Station. This software retrieves data from the monitor, performs error checking to ensure data integrity, and produces an output file in text format, which may be reviewed using Excel™. Macros are provided to facilitate the generation of several standard report formats.

Test Plug:

The test plug is a device that can simulate a sensor, or a cable and sensor, in order to provide the user with system diagnostic data. The test plug, when connected to the cable in place of a sensor, sends a constant electric signal to the monitor. If the monitor reads the electric signal, then the monitor and cable are functioning properly. Likewise, the test plug can be inserted directly into the monitor to deliver the constant current, and determine if the monitor is functional.

C. Contraindications

None

D. Warnings

- Operation of the CGMS requires the insertion of a Glucose Sensor into the skin. Infection, inflammation or bleeding at the Glucose Sensor insertion site are possible risks of glucose sensing. The Glucose Sensor should be removed if redness, pain, tenderness or swelling develop at the insertion site.

- The CGMS does not display glucose values and is intended to be used in addition to, not in place of, home glucose monitoring performed using a standard home glucose meter. During use of the CGMS, diabetes treatment should continue to be based on standard, periodic finger stick blood glucose measurements.

- Successful use of the CGMS requires some visual and auditory acuity. Use of the CGMS is not recommended for patients whose impaired vision or hearing does not allow full recognition of the monitor signals and alarms.

E. Precautions

- CGMS users should be trained to insert and replace Glucose Sensors, to program and operate the Glucose Monitor, and to respond to alarm conditions prior to attempted use of the system.

- Always wash hands with soap and water before opening the Glucose Sensor package. After opening the package, avoid touching any Glucose Sensor surfaces that will come in contact with the body (i.e., sensor, needle, connector adhesive surfaces and bandage).

- Before inserting the sensor, always clean the skin at the sensor insertion location with a topical antimicrobial solution, such as isopropyl alcohol.

- After sensor insertion, check the insertion location often for redness, bleeding, pain, tenderness and swelling, especially before going to bed in the evening and after waking up in the morning.

- Establish a rotation schedule for choosing each new sensor location. Avoid sensor locations that are constrained by clothing, accessories or subjected to rigorous movement during exercise.

- Monitors should be placed in ShowerPaks, prior to taking a shower or engaging in other activities in which the monitor would be expected to get wet. Do not submerge the monitor.

- Contact sports or other activities which may damage the monitor should be avoided. Prior to exercising, CGMS users should make sure that the sensor connector and monitor are securely fastened to their bodies.

- If the Glucose Sensor is disconnected and then reconnected again, the signals it sends to the monitor may not be stable or accurate. The sensor may need to be recalibrated and reinitialized before returning to normal operation.

- Users who also wear an insulin pump should make sure that the sensor insertion site is at least 3 inches from the insulin infusion site. Users who inject insulin should administer injections at least 3 inches away from the sensor insertion site.

- The Glucose Sensor is sterile in its unopened, undamaged package. Do not use any Glucose Sensor if its sterile package has been previously opened or damaged.

- The current and voltage signals shown in the monitor are to be used only for finding potential problems with the CGMS and do not directly indicate the current glucose value.

- If the monitor shows a "NO POWER" alarm for more than two (2) hours, the glucose data and program information in the memory will be lost. If this occurs, all program information will return to the manufacturer's default settings after the batteries are replaced. Users must first reprogram the monitor and then reinitialize and calibrate the sensor before returning to normal operation.

- Using the monitor in close proximity to strong electromagnetic sources such as medical imaging equipment, television and radio transmitters and high voltage power lines is not recommended.

IV. USE IN SPECIAL PATIENT GROUPS

The monitor has been clinically tested primarily in adult Caucasian persons with Type I diabetes. This device has not been tested in children. Because of variations in size and the amount of body fat, performance may be different in children relative to that observed when the device is used in adults. Although the system has not been studied in other diabetic patient populations, similar results are expected.

Use of the monitor may not be applicable for patients who are not motivated to operate it, are physically unable to operate it, have unrealistic expectations about its value and do not have a good support system at home for responding to alarms.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Periodic self-glucose monitoring using home glucose meters will provide information regarding variations in glucose levels, although not on a continuous basis.

VI. MARKETING HISTORY

The CGMS has not been marketed in any country.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Insertion of a Glucose Sensor into the skin may result in infection, inflammation or bleeding at the Glucose Sensor insertion site.

VIII. SUMMARY OF STUDIES

A. Laboratory Studies

1. Microbiological

(a) Sterility Assurance

The electron beam (EB) sterilization process used to sterilize the sensor assembly was validated according to the requirements of ISO 11137 Method 1.[1] A theoretical device bioburden of 19.7 colony forming units (CFUs) was calculated based on testing performed on ten devices from three different production lots. Based on these results, a total of 100 sensor assemblies were exposed to a sublethal dose of 6 kGy. All samples tested negative for surviving organisms following sterilization. These results indicate that the selected sterilization dose of 18.7 kGy will provide a sterility assurance level of 10^{-6}.

(b) Pyrogenicity

Pyrogenicity was assessed in rabbits using a USP XXII Pyrogen Assay.[2] Extracts were obtained from complete sensor assemblies. All testing performed indicated that the sensor assembly is non-pyrogenic.

2. Biocompatibility Testing

Several *in vitro* and *in vivo* tests were performed on glucose sensors and the polyurethane tubing which houses the sensor during implantation to determine the level of risk associated with the subcutaneous insertion of this device. Testing was based on the FDA's Tripartite Biocompatibility Guidance recommendations for a short-term tissue-contacting device.[3] The results of these tests are listed in Table 1:

Table 1: Biocompatibility Test

Test	Sensor	Tubing	Result
Intracutaneous Reactivity	x	x	non-reactive
Hemolysis (in-vitro, saline extract)	x	x	non-hemolytic
Mutagenicity (Ames test, saline extract)	x	*	non-mutagenic
Cytotoxicity (MEM elution, L-929 cells)	x	x	non-cytotoxic
Guinea Pig Maximization (saline, cottonseed oil)	x	x	weak sensitizer (Class I)
Subacute Toxicity (14 day intravenous dosing study in mice)	x	*	non-toxic
USP Acute Systemic Toxicity (saline, cottonseed oil)	x	x	non-toxic
USP Muscle Implantation (7 day)	x	x	no significant reaction
USP Muscle Implantation (30 day)	x	*	no significant reaction

* Mutagenicity, subacute toxicity, and 30-day USP muscle implantation testing was not conducted on the tubing since ISO-10993 states that these tests are not required for devices with short-term tissue contact.

3. Accuracy and Precision

Sensors were studied *in vitro* for accuracy and precision after calibration by placing the sensors in solutions with known glucose concentrations. These control solutions were quantified using a YSI 2700 SELECT® glucose analyzer (Yellow Springs Inc., Yellow Springs, Ohio) and a linear calibration curve was constructed (50 mg/dL, 150 mg/dL, 250 mg/dL and 350 mg/dL glucose). Accuracy and precision were determined by comparing calculated sensor glucose concentration to that of the YSI measured glucose concentration via a percent error calculation. The average percent error was determined for twelve sensors from three different manufacturing lots. The average error at each glucose concentration was also determined.

The average percent error between the YSI determined concentration and the sensor calculated concentration was 11.9%. A comparison of YSI glucose versus sensor calculated glucose values revealed an average correlation coefficient of 1.0, average y-intercept of 3.14 and an average slope of 0.96. The coefficient of variation was less than 6% for all sensors tested.

4. Stability

An evaluation of long-term sensor stability was performed by immersing sensors in a 100 mg/dL glucose solution for 96 hours. The output signal from the sensor drifted less than 13% during the test.

5. Interferences

Sensor response to ascorbic acid, acetaminophen, uric acid and oxygen was evaluated by placing sensors in phosphate buffered saline (PBS) solutions containing physiologically relevant concentrations of the potentially interfering substance. The sensor output current was monitored and compared to the output currents of the same sensor equilibrated in PBS. These studies indicated that there was no significant change in sensor output associated with exposure to these potentially interfering substances.

6. Electromagnetic Compatibility

Monitors were connected to test loads and tested for both electromagnetic emissions and immunity in accordance with the following test standards:

MIL-461/462D (magnetic emissions and magnetic immunity)[4]
EN 55011 (radiated emissions)[5]
IEC 61000-4-3 (radiated immunity)[6]

All devices met the requirements of these standards, confirming that the CGMS will not be adversely affected by normally encountered electronic equipment nor will the CGMS interfere with electronic equipment in close proximity to the device. During testing at levels higher than those specified in the standards, it was noted that incorrect signal values were displayed by the monitor when exposed to high intensity fields. As a result of this finding, the Instructions For Use for the CGMS was revised to state that the device should not be used in close proximity to sources of high intensity electromagnetic fields such as high power radio or television transmitters or high voltage power lines.

7. Electrostatic Discharge

Six functional monitors were subjected to electrostatic discharge testing according to the requirements of IEC 61000-4-2.[7] Contact (2, 4, 6 and 8 kV) discharges were applied to multiple points on the monitor. All test samples passed functional testing performed following exposure to these discharges.

8. Environmental Testing (Monitor)

(a) Mechanical Vibration

Six monitors were subjected to mechanical vibration testing using a random vibration profile for 10 minutes at 6.3 g RMS. Functional testing performed after vibration exposure confirmed that no units were damaged by this testing.

(b) Mechanical Drop

Six monitors were dropped from a height of 36 inches onto a linoleum covered concrete floor onto each of the device's six surfaces. All samples passed functional testing performed after the drops.

(c) Mechanical Shock

Six monitors were subjected to shock testing at a level of 1500 g's with a 0.5 millisecond pulse duration. One shock was applied in each axis (±x, ±y and ±z) for a total of six shocks per device. All samples passed functional testing performed after shock exposure.

(d) Temperature Shock

Twelve monitors were subjected to ten cycles of temperature shock at temperature extremes of -20° C and 70° C. Dwell time at each extreme was 30 minutes with transition between extremes at a rate of 20° C per minute. All samples passed functional testing performed after the monitors were allowed to stabilize at room temperature for at least 4 hours.

(e) Temperature/Humidity Exposure

Six monitors were exposed to 15° C (5% RH) for 24 hours followed by -5° for 96 hours. An additional six monitors were exposed to 50° C (5% RH) followed by 50° C (95% RH) for 96 hours. All samples passed functional testing performed after the monitors were allowed to stabilize at room temperature for at least 4 hours.

(f) Temperature Storage

Six monitors were exposed to -20° C for 24 hours followed by 55° C for 24 hours. An additional six monitors were exposed to -40° C for 24 hours followed by 70° C for 24 hours. All samples passed functional testing performed after the monitors were allowed to stabilize at room temperature for at least 4 hours.

(g) Shipping Test

Three monitors were packaged using standard materials and methods and subjected to an ISTA Project 1A shipping test. All samples passed functional testing performed at the conclusion of the test.

9. Stress and Wear Testing (Sensor)

(a) Solvent Resistance

Sixty-four sensor assemblies were visually examined after wiping with a 70% isopropyl alcohol sterile swab. All devices were confirmed to be free of any cracking, crazing or other irregularities caused by this exposure.

(b) Watertightness

Sixty-four devices were tested according to the requirements of CEI/IEC 529, watertightness designation IPX5/IPX7 (jetting water/temporary submersion).[8] All units tested met the specified requirements.

(c) Electrical Connection Test

Sixty-four sensor assemblies were evaluated by connecting the assembly to the sensor cable and measuring the resistance at each contact pad. In all cases, resistances were less than the specified maximum of 10 ohms.

(d) Latching Test

The force required to separate the sensor cable from the sensor assembly at the latch joint was measured for 64 sensor assemblies. In all cases, the force exceeded the minimum acceptable value of 10 pounds.

(e) Insertion Force

Insertion forces were measured for a total of 64 sensor assemblies by inserting the sensor into moistened chamois skin. In all cases, the insertion force was less than the specified maximum of 5 Newton. All samples were free of any damage associated with this insertion.

(f) Cap Pull Test

Sixty-four sensor assemblies were tested to evaluate the bond between the sensor cap and base. In all cases the gripper jaws pulled lose at forces exceeding 6.1 pounds without any separation of the cap from the base. These results confirmed that all bonds exceeded the specified minimum strength of 3.0 pounds.

(g) Needle/Hub Pull Test

Sixty-four sensor assemblies were tested to evaluate the strength of the bond connecting the sensor needle to the hub. A small number of the samples tested initially had separations forces which were below the specified minimum of 2.5 pounds. New qualification units were built using an improved needle/hub bonding procedure. All samples built using the new procedure exhibited bond strengths that exceeded 2.5 pounds.

10. Package Integrity Testing (Sensor)

(a) Burst/Creep Test

After exposure to Electron Beam sterilization, multiple drops from 36 inches, temperature and humidity cycling, temperature shock and aging at 55° C for 3 weeks, 20 pouches containing sensor assemblies were subjected to burst and creep testing.

The mean burst pressure was 97.2 inches of water with a range of 79.0 to 109.0 inches. During creep testing six of the ten pouches held 50% of the mean burst pressure for 30 seconds without bursting. The remaining four pouches burst at pressures between 46.3 and 49.8 inches of water at duration between 0 and 25 seconds. All bursts occurred at the bottom of the pouch and not at the top heat seal that is created after the sensor is inserted into the pouch.

(b) Dust Drum Package Challenge

After exposure to Electron Beam sterilization, multiple drops from 36 inches, temperature and humidity cycling, temperature shock and aging at 55° C for 3 weeks, 21 pouches containing sensor assemblies were subjected to dust drum package challenge testing.[9] All devices were free of microbial growth following dust drum exposure.

B. Animal Studies

1. Sensor Evaluation in Non-Diabetic Dogs

In vivo sensor response was evaluated during hyperglycemic clamps performed in four non-diabetic dogs. Each subject was inserted with up to four sensors in the neck area 3 hours prior to the clamp to allow acclimation of the sensors to the tissue environment. Once a baseline was established, a glucose load was initiated consisting of a glucose bolus followed by a variable glucose infusion to increase the plasma glucose from normal (~80 mg/dL) to approximately 180 mg/dL. Hyperglycemia was maintained for 2 hours, after which the glucose was allowed to return to normal by stopping the glucose infusion or forced to return to normal by infusion of additional insulin. An experiment was also conducted using somatostatin (an insulin secretion inhibitor) to prevent changes in insulin. All three experiments plus an additional control experiment (no glucose load) were performed in each dog (16 experiments in total).

One sensor in the control group was excluded from analysis due to a broken wire. In the remaining 15 sensors in the control group, a stable signal was observed 2-3 hours following insertion. The average *in vitro* sensitivity of all sensors was 0.4 ± 0.05 nA/mg/dL (n=63).

For all sensors, the retrospective calibrations based on the *in vivo* sensitivities resulted in sensor glucose dynamics that mirrored the plasma glucose dynamics. Delays between sensor and plasma glucose were ~5 minutes for experiments I and II and ~10 minutes for experiment III.

2. Evaluation of Subcutaneous Sensor Performance by Oral Glucose Tolerance Test in Diabetic Dogs

Experiments were performed in a total of three diabetic dogs. Diabetes was induced by steptozotozin (n=1) or pancreatectomy (n=2) 6 months or more prior to the experiments. Glucose was controlled by insulin injections based on multiple daily measurements (1-4 measurements per day).

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One sensor in the control group was excluded from analysis due to a broken wire. In the remaining 15 sensors in the control group, a stable signal was observed 2-3 hours following insertion. The average *in vitro* sensitivity of all sensors was 0.4 ± 0.05 nA/mg/dL (n=63).

For all sensors, the retrospective calibrations based on the *in vivo* sensitivities resulted in sensor glucose dynamics that mirrored the plasma glucose dynamics. Delays between sensor and plasma glucose were ~5 minutes for experiments I and II and ~10 minutes for experiment III.

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Experiments (n=5) consisted of insertion of two sensors in the neck area of each subject followed by 4 days of continuous monitoring.

All sensors performed well on the first day: however only 50% of the sensors survived until day three. This is believed to be due to non-observed subject activities during the night and the inability to adequately affix the sensor to the canine's skin (sutures were required).

Sensor sensitivity was observed to decrease over time. Day one *in vivo* sensitivity was not statistically different from *in vitro* sensitivity (0.17 ± 0.02 vs. 0.15 ± 0.02) whereas the sensors which survived until explantation (n=6) had lower *in vivo* sensitivities compared to the initial *in vitro* sensitivity (0.22 ± 0.10 vs. 0.17 ± 0.15).

C. Clinical Studies

1. Evaluation of Sensor Design and Sensitivity (GS-001)

This study was conducted to provide an initial assessment of safety and efficacy of the CGMS and to generate information that would help guide the design of future clinical trials. The study involved 11 subjects between the ages of 18 to 65 years with insulin dependent diabetes mellitus (IDDM) of a duration of less than 15 years and one non-diabetic volunteer. Each subject was evaluated over a 96-hour period.

During each day of the study, 25 blood glucose measurements were taken using a YSI reference meter. An additional six finger stick (capillary blood) measurements were taken each day using a standard Home Glucose Meter. Subjects were administered ascorbic acid and acetaminophen during the study to evaluate any potential effects on the performance of the sensor.

One subject experienced redness and induration at the insertion site while the sensor was in place that was successfully treated with antibiotics. All sensor insertion sites were examined 1 week after sensor removal and in all cases the sites had healed completely and without complication.

Significant variability in sensor performance was observed during the study with the sensor effectively tracking blood glucose measurements in approximately 50% of subjects. Administration of ascorbic acid or acetaminophen did not appear to affect sensor performance. Cases of poor sensor performance were attributed to issues with the adhesion of the sensor's outer membrane, moisture resistance of the cable that connects the sensor to the monitor and the effect of radiation sterilization.

2. Sensor Feasibility Study (GS-002)

This study was conducted to evaluate improvements to the CGMS implemented based on the results of the initial feasibility study. Improvements included use of a 22-gauge needle for insertion, elimination of the need for a preconditioning step and elimination of

the need for pre-calibration. The study involved 12 subjects between the ages of 18 and 65 years with IDDM (duration of 25 years or less) and followed the same protocol used for GS-001.

Performance of sensors evaluated in this study fell into four general categories: 1) noisy output and low sensitivity, 2) good correlation with reference values for 24-48 hours, 3) good correlation with reference values until lead failure and 4) good correlation with reference values until the sensor was removed. Use of the sensor did not cause irritation, redness or soreness in any subjects. All insertion sites were examined 1 week after sensor removal and were confirmed to have healed completely and without complication.

3. Evaluation of Sensor Against Previously Studied Monitoring System (GS-003, Phase I)

This study was intended to evaluate improvements implemented based on the results of GS-002. These improvements included 1) reduction of noise in the sensor circuit, 2) reduced time for *in vivo* equalization, 3) improved outer membrane, 4) addition of hypoglycemia alarm and 5) addition of *in vivo* calibration.

The study involved 22 subjects between the ages of 18 and 65 years with IDDM (duration of 25 years or less). Each subject had one or more sensors inserted along with a heparin-lock to allow withdrawal of samples for blood glucose testing. Sensors were worn and data collected for a period of up to 96 hours. Venous blood glucose measurements were taken using a YSI glucose meter and capillary glucose measurements were taken using a standard Home Glucose Meter.

There were no adverse effects associated with any of the 52 sensor insertions performed. The average useful life of the sensors was 62 hours. The values from the sensor demonstrated a high level of correlation with the YSI reference values (R=0.80).

4. Evaluation of Sensor Against Previously Studied Monitoring System (GS-003, Phase II)

This study was intended to compare the performance of the improved monitor to that of the monitor used in prior feasibility studies. A total of four subjects participated. Each subject had two sensors inserted, with one connected to the updated monitor and the other to the previous prototype monitor. Sensor data were recorded for a period of up to 4 days. Venous blood glucose was measured periodically using a HemoCue or YSI reference meter. Finger stick (capillary) measurements were obtained using a standard Home Glucose Meter.

Glucose values from both the original and improved monitors showed high (0.9) correlation with the reference venous and capillary values. Although both monitors demonstrated similar correlation with the reference meter values, data collected from the earlier version monitor were more variable and noisier.

5. GS-004, Phase IA

This study was conducted to further evaluate the performance characteristics of the CGMS. The study involved five diabetic subjects with each subject wearing two sensors and monitors. Subjects were also fitted with a heparin-lock catheter to facilitate withdrawal of venous blood samples. Sensors were calibrated using capillary blood glucose values measured with a standard Home Glucose Meter. Periodic venous glucose measurements were obtained using a YSI reference meter.

Of the 14 sensors inserted during the study, 3 failed to accurately track blood glucose due to low sensitivity. Data from the remaining sensors were plotted against the reference venous and capillary glucose values. The data for the CGMS displayed a high degree of correlation with the reference venous and capillary values (R=0.77).

6. GS-004, Phase IB

This study was intended to assess the ability of the CGMS to track blood glucose levels and to assess its function as a hypoglycemia alert device. The study involved 15 diabetic subjects. All subjects had a glucose sensor inserted by a nurse practitioner. Subjects were instructed to keep the sensor in place for up to 4 days and to perform finger stick blood glucose measurements on a routine basis during this period. The hypoglycemia alarm was set to 80 mg/dL during the evaluation.

Three subjects received two sensors whereas the remaining 12 subjects used one sensor during the study period. The average sensor life was 89 hours. A total of 68 hypoglycemic episodes were identified by the finger stick glucose measurements, the sensor correctly identified 58 of these events. A correlation plot of sensor data versus finger stick data was generated and the correlation coefficient was approximately 0.8.

7. GS-004, Phase II (Multicenter Study)

(a) Overview

This study was intended to provide data in support of the following two primary hypotheses: 1) the output of the CGMS will accurately depict the trends, over time, in subject's glucose values as compared to periodic glucose measurements obtained from a standard Home Glucose Meter and 2) the CGMS will produce a hypoglycemia alarm when the subjects blood glucose (as measured by the Home Glucose Meter) drops below the physician set limit. Secondary study objectives included assessment of the useful sensor life and comparison of performance as a function of health care versus user insertion.

(b) Inclusion Criteria

The study was conducted at four geographically varied investigational sites and involved a total of 62 subjects. Each site enrolled at least 15 subjects. Subjects were required to be at least 18 years old, to have diabetes mellitus, and to be free of any severe skin abnormality or significant concomitant illness to be considered for inclusion in the study.

(c) Subject Demographics

Of the 62 subjects participating in this study, 30 were male and 32 were female. The average subject age was 44 years. The majority of subjects (58) had Type I diabetes whereas the remaining 4 subject has Type II diabetes.

(d) Study Procedures

Following study enrollment, subjects were trained in the use of the CGMS and associated study procedures. A sensor was inserted in the abdominal area by the medical staff of the investigational center and subjects were allowed to return home for a period of up to 4 days or until the first sensor required replacement. Subjects returned to the investigator to have their second sensor inserted and were provided an additional sensor to insert themselves at home. Each subject was scheduled to have a minimum of five to a maximum of ten sensors sequentially inserted at scheduled 4-day intervals for a maximum duration of 20 days. Subjects were instructed to check their blood glucose at least 11 times per day using a standard Home Glucose Meter (Accu-Chek Advantage). Subjects were instructed to also check their blood glucose whenever a hypoglycemia alert occurred and every 15 minutes thereafter, until the hypoglycemic event resolved.

(e) Devices Utilized

The 62 subjects wore a total of 415 sensors during the study. Thirty-nine of the inserted sensors did not contribute data due to failure to produce electrical contact at the time of insertion. On the average, each subject used 6.7 sensors during the study. The median useful sensor life was 69 hours and the average useful life was 64 hours.

(f) Adverse Events

A total of eight adverse events were reported during the study. Only one of these events was described by the investigator as serious. This event involved a subject who experienced severe hypoglycemia due to a treatment error in the administration of insulin. Since the CGMS did not provide any glucose concentration information to subjects during the study, the investigator determined that this event was unrelated to the use of the CGMS.

The remaining adverse events were classified as moderate (2) or mild (5) and were associated with either discomfort or bleeding at the sensor insertion site.

(g) Subject Discontinuations

Three subjects withdrew from the study prior to completing the specified monitoring period. In one case, the subject withdrew due to an unexplained rash and bleeding at the sensor insertion site. In the second case, the withdrawal was due to an unexplained rash and discomfort at the insertion site. The third subject did not complete the study as a result of unstable retinopathy with retinal bleeding. In the investigator's opinion, the retinopathy was unrelated to the use of the CGMS.

(h) Insertion Site Examinations

A total of 380 sensor insertion site examinations were documented during the study. Three-hundred-thirty-four (85%) of these examinations were reported as normal. A summary of the remaining 56 site examinations reported as abnormal is provided in Table 2.

Table 2: Abnormal Sensor Site Examinations

	Frequency
Redness	36
Redness & Rash	3
Rash	1
Other:	
Small red "freckle like" dot	6
Papules	2
Bruise	2
Bleeding	2
Tape irritation	2
Unknown	2
Total abnormal observations	*56*

Twenty-one of the abnormal site examinations were attributed to skin irritation caused by the commercially available occlusive dressings used to secure the sensor to the subject's body. In all cases, subjects recovered without incident and follow-up assessments confirmed that all sites returned to normal after sensor removal.

(i) Device Complaints

A summary of device-related complaints reported during the study is provided in Table 3.

Table 3: Device Related Complaints

Device Complaint or Alarm Message	Complaint Description	Number of Subjects Reporting Event	Total number of events
Too High Alarm	Wet equipment	13	20
Disconnect Alarm	Sensor connection to the cable was disrupted.	7	10
No Contact	The sensor did not make an appropriate contact with the cable.	7	8
Disposable Problem	The introducer needle or sensor platform was defective resulting in poor insertion or no insertion.	7	8
Low Sensor Sensitivity	The electrical current output by the sensor dropped below the sensitivity threshold.	4	4
Sensor Dislodged	The sensor became dislodged from the subcutaneous tissue. No functional problem with device was noted.	4	4
Computer Download Problem	The data from the sensor were not successfully transferred to a personal computer-resulting in data loss.	3	3
Clinical Complaint	The sensor insertion caused minor reaction such as bleeding, rash and discomfort.	2	2
Calibration Problem	The sensor did not calibrate effectively.	1	1
Patient Error	The patient inadvertently turned the monitor off.	1	1
Damage To Unit	During a shower, the monitor was inappropriately protected and the monitor was damaged by water.	1	1

(j) Effectiveness Data

1. Application of Regression Calibration to Clinical Data

The design of the clinical study required subjects to collect at least 11 reference meter measurements per study day. In order to evaluate the linear regression calibration technique used in the CGMS, these reference values were divided into a calibration

set and an evaluation set. The calibration set was defined as the four meter values patients with diabetes typically take to control their blood glucose: before breakfast, lunch and dinner and at bedtime. These specific blood glucose tests were identified by time of day. For each study day, the blood glucose value closest to 7:00 a.m., 12:00 p.m., 7:00 p.m. and 10:00 p.m. were identified as the calibration set. If a sensor was inserted or removed midday, only calibration values taken while the sensor was in use were assigned to that sensor. The evaluation set consisted of all remaining blood glucose values taken that day.

The regression calibration was performed using SAS statistical software. For each day of sensor use, the resulting regression slope and offset were calculated. If the calibration slope was between 2 and 10, then the calibration was used to convert each 5-minute CGMS electrical reading into a glucose value. The calibration was applied to all CGMS values obtained during that day. If the slope was outside the allowable range or if no calibration blood glucose values were identified for that day, then the CGMS glucose values were not calculated.

The regression calibration was attempted with a total of 1,153 sensor days. Of these, 1,016 days had both sensor and reference data and could be calibrated. Table 4 gives the distribution of the number of calibration values used in each regression calibration. The majority of calibrations (60%) were performed using three or four meter values. Note that because the regression equations utilize fixed intercepts (either 0 or 3 nA), only one meter value is required to perform the calibration. For 19 days, none of the reference meter values fell close enough (within 2 hours) to the calibration target time to be identified as a calibration value.

Table 4: Number of Regression Calibration Values Per Sensor Day

Number of Calibration Values	**Number of Sensor Days**	**Percent**
0	19	1.87%
1	148	14.57%
2	227	22.34%
3	248	24.41%
4	374	36.81%

2. Sensor Accuracy

In order to evaluate the performance of the CGMS, a data set of paired CGMS-reference meter values was created. Each reference value was paired with the average of all CGMS values taken within 5 minutes of the reference. In most cases there were two CGMS values within 5 minutes of the reference measurement, but the number of CGMS values ranged from zero (no valid sensor values were available) to three (if the timestamp of the meter value was identical to the timestamp of a sensor value). These paired data points formed the basis of all subsequent analyses.

Because the labeling of the CGMS limits the use of a single sensor to 72 hours, only data from that timeframe were analyzed. A total of 6,207 paired data points were obtained for the first 72 hours of sensor use during the clinical study. Of these, 2,186 were identified as calibration values (i.e., were closest to the four calibration target times). The remaining 4,021 reference values were used as evaluation values. Two restrictions were placed on the reference values. First, only reference values within the sensor operating range of 40 to 400 mg/dL were analyzed. Second, in order to minimize the possibility of statistical dependency among reference values, if two reference measurements were taken within five minutes each other, only the latter of the two was analyzed.

The average difference score for the 4,021 evaluation pairs based on the regression calibration is -5.4 mg/dL +/- 44.2 (range: -274 to 233). Table 5 provides a breakdown of the averages for the three days of sensor use. Standard deviations appear in parentheses. Table 6 presents difference scores stratified by day of use, type of insertion and site.

Table 5: Average Difference Scores by Day (in mg/dL)

Day 1	-5.4 (43.4)
Day 2	-3.8 (44.9)
Day 3	-7.8 (44.5)
Overall	**-5.4 (44.2)**

Table 6: Average Difference Scores for Insertion Type, Day of Use and Site (in mg/dL)

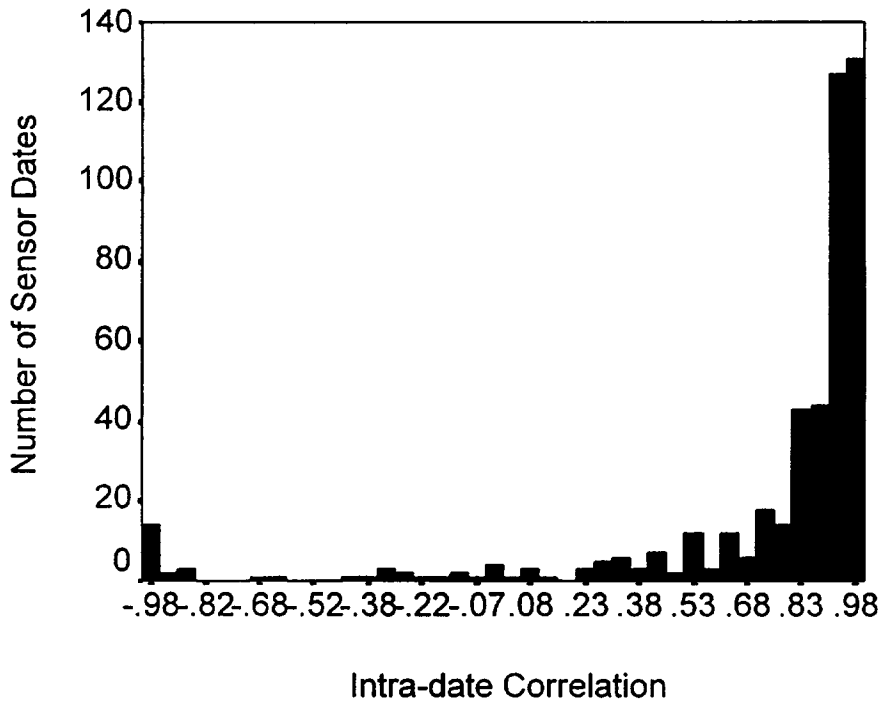
Medical Professional Insertion				
	Day 1	Day 2	Day 3	Total
Site 01	-5.6	-3.5	-3.5	-4.3
Site 02	-6.7	-3.3	-4.2	-5.1
Site 03	-0.04	-2.1	-5.4	-2.4
Site 04	-7.0	-10.3	-18.6	-10.6
Total	-4.9	-4.5	-6.6	-5.2

Patient Insertion				
	Day 1	Day 2	Day 3	Total
Site 01	2.5	0.4	-0.8	0.9
Site 02	-8.9	-5.9	-9.3	-8.0
Site 03	-8.6	-4.1	-12.7	-7.7
Site 04	-3.9	-1.0	-17.4	-5.3
Total	-5.9	-3.0	-9.8	-5.6

3. Intra-Date Correlation

Separate daily correlation values were calculated for each calendar date on which the sensor was used. The median value was 0.92, with 75% of the correlation values above 0.75. Figure 1 presents the distribution of intra-date correlation values based on the regression calibration.

Figure 1: Distribution of Intra-Date Correlation Coefficients



4. Categorical Agreement

Each reference value and each sensor value was categorized as being Low, In Control or High relative to a desired range of glucose control (70 to 180 mg/dL). To avoid potential lack of agreement due to the reference or sensor value being close to one of the boundaries, all pairs where one or both of the values fell within 20% of the boundary were excluded from the analysis of categorical agreement. As a result of the use of the exclusion regions surrounding the boundaries, values less than 56 mg/dL were considered Low, those between 84 and 144 were considered In Control and values above 216 were classified as High.

A 3 x 3 cross-tabulation of the number of pairs of data falling into each of the nine sensor-reference category combinations is provided in Table 7. The three cells on the diagonal represent agreement, with the off diagonal cells representing varying degrees of disagreement.

Table 7: Categorial Agreement (in mg/dL)

Meter Category	CGMS Category			
	Low (<56)	In Control (84-144)	High (>216)	Total
Low (<56)	50	25	0	75
In Control (84-144)	117	930	13	1060
High (>216)	2	42	332	376
Total	169	997	345	1511

Of the 75 reference values in the Low category, 66.7% (50) were identified by the sensor. Of the 169 sensor values in the Low category, 29.6% (50) were confirmed by the reference meter. Of the 376 reference values in the High category, 88.3% (332) were identified by the sensor. Of the 345 sensor values in the High category, 96.3% (332) were confirmed by the meter.

5. Evaluation of Calibration Criteria

Two trained independent experts subjectively analyzed sensor results from all patients by visually comparing the sensor trends to glucose meter trends and then categorizing the comparisons as either good matches or poor matches. Receiver operator curves were generated to correlate these categorical comparisons with regression statistics, including the correlation coefficient and mean absolute error. The cut-off points established to identify sensor tracings with optimal accuracy were a correlation of .79 or higher, and a mean absolute error of 28% or lower. Categorical agreement by matched pairs of sensor and meter values for Low, In Control, and High results was analyzed and supported these cut-offs.

6. Hypoglycemia Alert

A total of 519 meter readings fell below the hypoglycemia limit in use at the time of the measurement. The CGMS recognized these hypoglycemia events with 81% accuracy. Of the 697 CGMS readings below the selected alert limit, 279 (60%) represented hypoglycemia according to the reference method, with a 40% rate of false positives. Because of this performance, the hypoglycemia alert feature has been removed from the system.

IX. CONCLUSION DRAWN FROM THE STUDIES

A series of *in vitro* qualification tests performed on the components of the CGMS have demonstrated the mechanical integrity of these components and their ability to withstand

stresses encountered during normal use. Both *in vitro* and *in vivo* testing have confirmed that the CGMS is capable of detecting and recording trends in interstitial glucose concentrations. Evaluation of glucose trends recorded by the CGMS in conjunction with glucose concentrations measured with a standard home glucose meter has demonstrated that the CGMS may provide useful additional information which allows identification of patterns of glucose level excursions above or below the desired range. Adverse effects have been limited to irritation or bleeding at the sensor insertion site. There have been no severe adverse effects associated with the use of the CGMS.

The results of *in vivo* and *in vitro* testing provide reasonable assurance that the MiniMed Continuous Glucose Monitoring System is safe and effective for its intended use when utilized in accordance with the product labeling.

X. PANEL RECOMMENDATIONS

A meeting of the Chemistry and Toxicology Devices Advisory Panel was held on February 26, 1999, to discuss the PMA. The Panel voted unanimously recommending approval of the PMA subject to the following conditions:

- Submission of additional data analyses regarding interference, e.g., bilirubin, triglycerides, medications, etc.
- Labeling changes to the operation manual and additional patient education information.
- Submission of additional data analyses regarding the validation of the calibration algorithm.
- Additional studies to gather data from the use of the device in various patient groups not previously selected for study:

  Type II diabetics,
  Children with diabetes,
  Gestational onset of diabetes,
  Diabetics with concomitant disease states,
  Long- and short-term duration diabetics,
  Non-Caucasian diabetics.

The Panel was divided over the last condition, with most favoring a post-market study requirement and the remaining favoring a pre-market study requirement.

Following the February 26, 1999, panel meeting, the applicant submitted two amendments to the PMA. The first amendment, dated April 7, 1999, responded to deficiencies cited in the March 18, 1999, post-panel status letter and the February 9, 1999, major deficiency letter and contained revised labeling based upon modifications agreed upon at the real-time labeling modification meeting on March 23, 1999. The second amendment, dated May 10, 1999, provided two tables which compared the categorical agreement of data from the successful calibrations to data from unsuccessful calibrations.

CDRH 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 and issued an approval letter on June 15, 1999.

A GMP inspection of the applicant's sterilizing site was conducted on March 25, 1998, and a final inspection of the manufacturing facilities was conducted on June 4, 1999. Both sites passed inspection and it was determined that the firm has an acceptable GMP program.

XI. 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

XII. BIBLIOGRAPHY

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4. U.S. Military Standard: Electromagnetic Emission and Susceptibility Requirements for the Control of Electromagnetic Interference/Measurement of Electromagnetic Interference Characteristics.

5. European Norm: Limits and Methods of Measurement of Radio Disturbance Characteristics of Industrial, Scientific and Medical (ISM) Radio-Frequency Equipment (1991).

6. International Electrotechnical Commission Standard: Testing and Measuring Equipment - Electrostatic Discharge Immunity Test (1995).

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8. International Electrotechnical Commission Standard: Degrees of Protection Provided by Enclosures (1989).

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