SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Continuous subcutaneous glucose monitoring system
Device Trade Name:	Guardian Telemetered Glucose Monitoring System (TGMS)
Device Procode:	MDS
Applicant's Name and Address:	Medtronic MiniMed 18000 Devonshire Street Northridge, California 91325
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P980022/S010
Date of Notice of Approval:	January 7, 2004
Expedited:	*Not applicable*

II. INDICATIONS FOR USE

The original PMA (P980022) was approved on June 15, 1999, with the following indication:

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.*

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the continuous glucose monitoring system.

The Guardian Telemetered Glucose Monitoring System (TGMS) is indicated for continuous or periodic monitoring of interstitial glucose values in persons with diabetes mellitus. Glucose values calculated by the device will be used to trigger hypo- and hyperglycemia alerts but glucose values will not be displayed. Up to 21 days of stored data can be downloaded to a personal computer to identify patterns and optimize diabetes management.

III. CONTRAINDICATIONS

Use of the Guardian TGMS is not recommended for persons whose impaired vision or hearing does not allow full recognition of the Guardian TGMS signals and alarms/alerts.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Guardian Telemetered Glucose Monitoring System (TGMS) labeling.

V. DEVICE DESCRIPTION

The TGMS consists of a Transmitter (model 7700) that is connected to the glucose sensor, and a Monitor (model 7600) which receives and stores information from the transmitter. The system uses the same glucose sensor (model 7002) as the CGMS that was approved in the original PMA, P980022. The TGMS system utilizes a new version of PC software (MiniMed model 7315 Solutions TGMS Software) used in conjunction with the current model 7301 Com-Station to download information stored in the Monitor for display on a personal computer.

The primary differences between the TGMS and originally approved CGMS are:

1) the use of RF telemetry (rather than a cable) to transmit information from the sensor to the Monitor;
2) the use of a real-time (rather than retrospective) calibration algorithm; and
3) the addition of programmable hypo- and hyperglycemia alerts.

The TGMS requires an initial calibration two hours after sensor insertion. Calibration is based on glucose measurements performed using any FDA cleared glucose meter. The Monitor will alert the user to recalibrate 6 hours after the previous calibration was performed. If more than 12 hours elapse since the last calibration, the Monitor will no longer convert sensor values to glucose values until a new calibration value is entered.

Description of System Components

1. Model 7600 Monitor

The model 7600 Monitor is intended to function as a user interface. It is the information display for the TGMS, providing data storage and serving as an interface between the transmitter and a PC. The device provides alerts, which can be set by the user to alarm when the user's glucose levels enter either the preset hypo- or hyperglycemia ranges.

The Monitor receives telemetered glucose data from the transmitter, tags the data with the date and time, and processes and stores the information in nn-volatile memory. Data stored in the Monitor may be downloaded via infrared serial port to a PC for display of patient glucose data in tabular or graphical format.

The Monitor also functions as a user interface to control the setup and operation of the TGMS. Buttons on the face of the Monitor allow the user to input the date, time, patient data, and serial number of the transmitter being used. The date, time and other operating information are displayed on a backlit LCD panel. Audio and vibratory alarms provide feedback to the user when input or other errors are detected.

The Monitor is housed in a small, pager-sized, portable and wireless plastic case. Two AAA alkaline batteries provide an expected minimum operating life of one month that power the device. Circuitry for the unit is located on four printed circuit board assemblies (PCBAs). The Monitor also contains a piezo speaker to generate audio alerts and a vibrator motor that provides vibratory alerts.

2. Model 7700 Transmitter

The model 7700 Transmitter consists of a small, teardrop shaped plastic case, housing a battery pack and 2 printed circuit board assemblies. A cable, about 3 inches in length, extends from one end of the case and terminates in a connector that mates with the MiniMed model 7002 glucose sensor assembly. Insertion of a glucose sensor assembly into the sensor connector closes a switch, which connects three 1.5 volt silver oxide cells to the PCBAs and activates the transmitter. These cells are non-replaceable and intended to last the life of the unit, which is approximately one year under anticipated normal use conditions.

The transmitter case houses two PCBAs. One of these PCBAs contains a sensor potentiostat, a current-to-frequency converter, a microprocessor, and a real-time clock. The potentiostat applies power to the glucose sensor assembly, which in turn produces an electrical current representative of glucose concentration. The microprocessor accumulates sensor frequency counts every minute that are filtered and a weighted average produced at each five minute interval. The other PCBA contains a commercially available hybrid transmitter and an antenna. The transmitter hybrid uses an oscillator to generate a RF signal which is applied to an antenna integral to the assembly.

The RF message contains a unique transmitter ID, the sensor data, additional diagnostic information, and cyclic-redundancy check information to ensure the Monitor receives the data correctly. To further enhance integrity of the message, each Transmitter transmits at a pseudo-random time interval known to the Monitor such that the Monitor only listens for a message at the exact moment the corresponding transmitter is transmitting. The

Transmitter is attached to the skin using a double-sided, medical grade adhesive pad (model 7006).

3. Model 7315 Solutions TGMS Software

When used in conjunction with the MiniMed model 7301 Com-Station, the model 7315 Solutions TGMS Software facilitates the download and display of information stored in the model 7600 Monitor.

Modifications to Original Device

1. Monitor

The TGMS Monitor uses a real-time (rather than retrospective) calibration algorithm to convert electrical signals from the sensor to glucose concentrations. The Monitor incorporates hypo- and hyperglycemia alarms that can be set by the user. The hypo alert limit may be programmed from 40-100 mg/dL and the alarm is triggered if the glucose value calculated by the TGMS is equal to or less than the selected limit. The hyper alert may be programmed from 105-400 mg/dL and the alarm is triggered if the calculated glucose value is equal to or greater than the selected limit. The addition of the hypo- and hyperglycemic alerts are intended to enable identification and resolution of mild events before they become severe.

2. Transmitter

The TGMS Transmitter uses radio frequency (RF) telemetry at 418 MHz (rather than a cable) to transfer information from the Sensor to the Monitor. In the original CGMS, the electrical signals from the Sensor are processed in the Monitor and an average value is stored in the Monitor memory every five minutes. In the TGMS, signal processing occurs in the Transmitter. Every five minutes, the calculated average Sensor signal is transmitted via a digitally encoded RF signal to the Monitor. The Monitor then performs additional signal processing and stores the signal in memory and converts the Sensor signal to a corresponding glucose concentration based on the current calibration algorithm value.

Eliminating the cable connecting the sensor to the Monitor provides the user with more flexibility with respect to placement of the Sensor and Monitor. This will also facilitate bathing by allowing the Monitor to remain outside the shower, eliminating the need to place the Monitor in a protective bag. Additionally, the Transmitter in the TGMS is watertight and designed to remain attached to the user while showering.

3. Calibration Algorithm

The calibration algorithm for the TGMS system consists of three modules: 1) a filtering scheme that optimizes the glucose response of th Transmitter and reduces noise; 2) a calibration slope that converts the glucose response to interstitial glucose concentration; and 3) a system called the Self-Adjusting Gaussian Algorithm (SAGA) that identifies the need to replace the glucose sensor, removes outliers, and resets the calibration parameters as necessary.

The filtering scheme consists of both a finite impulse response (FIR) filter in the Transmitter and a Gaussian filter in the receiver. The FIR filter weights eight 1-minute sensor glucose reading counts from the sensor and the receiver then uses the Gaussian filter to weight eight 5-minute sensor readings from the Transmitter. The weights of the FIR filter are determined empirically while the weights of the Gaussian filter are determined by minimizing the noise in a 40-minute window.

The raw sensor data from 10 to 15 minutes following the entered SMBG measurement is paired to the SMBG value to optimize the calibration process. The calibration first pairs the SMBG value to the raw data and then calculates the slope using Gaussian Weighted Linear Regression (GWLR). The GWLR uses a maximum of 10 sensor-meter pairs and each pair is weighted accordingly to its temporal distance from the current time. The SAGA continuously calculates the Gaussian slope and continuously compares sensor-meter pairs, thus optimizing sensor performance.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

There are several other alternatives for the management of diabetes. Periodic self-glucose monitoring using home glucose meters will provide information regarding variations in glucose levels, although not on a continuous basis. Additionally, adult patients may use the original CGMS to record continuous interstitial glucose information although the CGMS does not have hypo-hyper alarm capabilities.

The Cygnus GlucoWatch is currently available as a minimally invasive device that provides hypo- and hyperglycemia alerts similar to the TGMS. The GlucoWatch also displays real-time values, which the TGMS does not.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

As of January, 2004, the TGMS has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Insertion of a Glucose Sensor into the skin may result in infection, inflammation or bleeding at the Glucose Sensor insertion site. Inappropriate alarms provided by the TGMS could result in inappropriate treatment decisions resulting in exacerbation of the symptoms associated with hypoglycemia and hyperglycemia.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

Simulated Use Testing for Precision and Accuracy

Two in vitro simulated use studies were conducted to verify the accuracy and precision. In one study, the units were calibrated and placed in standardized glucose solutions, which were varied to simulate the glucose excursions that may be seen during normal use. In the second study, the units were calibrated and placed in standardized glucose solutions in ascending steps of concentration. For both studies, the glucose solutions were validated using the YSI Glucose Analyzer and communication between the Monitor and the Transmitter was maintained for the duration of the testing. The collected data was used to calculate the precision and accuracy of the units tested.

Environmental Qualification

The Monitor and Transmitter were subjected to extensive environmental testing to verify that the device would continue to function properly, even when exposed to environmental stresses that exceed those anticipated during normal use. The testing included vibration, drop chemical exposure, operation at temperature and humidity extremes, storage at extreme temperature, temperature shock, splash and immersion testing, mechanical shock, shipping tests, and operating pressure.

Electromagnetic Compatibility (EMC) Qualification

EMC testing of the Monitor and Transmitter components of the TGMS included emission and immunity conducted in accordance with applicable FCC, military and international standards to ensure that there will be no adverse effect on function as a result of electromagnetic signals in the environment and that the TGMS will not emit signals that will adversely impact nearby equipment.

Potential for Interfering Transmissions and Corrupted Data

The potential for interference from both licensed and unlicensed transmitters was evaluated by risk assessment and implementation of design features to reduce the potential of corruptible data. Specifically, the following conditions were evaluated: 1) corruption of glucose data presented to the user, 2) occasional loss of a data packet due to interference from an intermittent or periodically transmitting source, or 3) complete loss of communication due to interference from a continuously transmitting source. The system includes design elements that adequately address these conditions. Additionally, any time data is lost, an alarm will notify the user with visual, audio, and/or tactile feedback.

Transmission Collision Testing

Testing performed to evaluate the effect of multiple TGMS Transmitters and Monitors operating in close proximity demonstrated infrequent missed transmissions occurring from

these circumstances. When missed transmissions do occur, the user is notified visually by a flashing icon. If two consecutive transmissions are missed, the Monitor will beep an attempt to re-synchronize with the Transmitter. If re-synchronization fails, the Monitor will issue an audible alarm and/or vibrate.

Battery Life Testing of Transmitter and Monitor

Accelerated testing was performed to confirm that the batteries used in the Transmitter will provide a device service life of at least one year and in the Monitor for at least one month under anticipated typical use conditions.

Software Evaluation

Design specifications, traceability analysis, development information, validation and verification and revision level history information were provided for the Monitor, Transmitter, and Read Memory, and Model 7315 Solutions Software.

Human Factors Studies

A detailed analysis of tasks necessary to use the device was conducted and confirmed that the design of the TGMS hardware and software minimizes the potential for user errors.

Alarm and Alert Evaluation

An evaluation of the decibel levels of the monitor alarms and alerts was also evaluated. Alarms are defined as audible beeps that signal the user to certain errors, whereas the term "alert" is used to indicate the audible sounds and vibrations that can be set by the user for hypo and hyper alarms. The alerts can be set at different volumes (there is a low, mid and high option), with or without vibration (user choice), and they can be turned on or off (also user choice). They can also be set at a range of low and high glucose ranges, to suit the user's need (as determined by the user and user's physician to be the "optimal" settings for an individual user). The alerts increase in volume every few minutes until the "siren alarm" is triggered after 10 minutes without being cleared by the user. The User Guide contains a contraindication that states, "Use of the Guardian is not recommended for persons whose impaired vision or hearing does not allow full recognition of the Guardian signals and alarms/alerts."

The evaluation was conducted on 23 production devices where the audible output levels were recorded at two distances (10 cm and 100 cm). The 100 cm distance was indicated as the distance that would approximate the distance between a sleeping patient and the monitor sitting on an adjacent night stand. The testing included the 4 types of alarms; standard alarm, hypo alert, hyper alert, and siren alarm. The collected data showed the average sound intensity for each type of alarm. Based on a literature search undertaken to find information on arousal from sleep due to auditory stimuli, the evaluation showed that taking into account the variable intensity and frequency of the alarms and the motivation of the user, the audible alarms of the CGM during intended use are adequate to awaken the average sleeping user within a period of time that is acceptable to safely correct the problem causing the alarm.

Adhesive Patch Feed Back

Information taken from an in-house study was analyzed to verify the efficacy of the transmitter foam patch adhesive for its ability to adhere and for comfort.

Calibration Algorithm Development and Evaluation

A simulated study of the TGMS was conducted suing data collected in an in-house clinical study of the CGMS system. A total of 44 subjects, of which 12 were diabetic, participated in the study. Subjects were requested to perform four to six fingerstick blood glucose measurements per day. The sensor data and meter values were retrospectively analyzed using the TGMS real time calibration algorithm. Except for the first meter value entered for calibration, each subsequent value was compared to the calibrated sensor output, prior to being used to update the sensor calibration. A total of 279 meter blood glucose measurements were paired with a corresponding sensor glucose value, resulting in a MAD of 18.5%. Clark Error Grid Analysis indicated that 97.8% of the paired values fell within the A and B regions.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

1. Performance Evaluation of the TGMS in Persons with Diabetes Mellitus, Protocol GS029

An in-house study was conducted to collect glucose data from the TGMS to evaluate real-time calibration algorithms and assess alarm performance in subjects with either Type 1 or Type 2 diabetes. A total of 15 subjects between the ages of 22 and 61 years of age each wore one sensor and took frequent blood glucose measurements throughout the day over a period of 2 weeks. A minimum of 7 and maximum of 12 fingerstick measurements were performed by each subject in a 24 hour period. The hypo- and hyperglycemic alarm function was turned off during week one and turned on during week two.

To evaluate performance, a total of 703 meter blood glucose values were paired with TGMS values from a total of 61 sensors. Sensor values ranged from 40-400 mg/dL and meter values ranged from 27 to 403 mg/dL. Four indices of numerical agreement were calculated to evaluate performance of the TGMS: correlation, regression, MAD, and Clarke error grid analysis. The performance of the hypo- and hyperglycemic alarms was evaluated by calculating sensitivity, specificity, and false positive and false negative rates, using meter values to indicate true absence or presence of a glucose excursion.

Results

A. Sensor Performance with Hypoglycemic and Hyperglycemic Alarm Turned Off (N= 32 sensors)

During Week 1 of the study, subjects wore sensors with the hypo- and hyperglycemic alarms turned off. A total of 32 sensors were evaluated with alarms turned off. A total of 311 meter blood glucose values were paired with a sensor value.

The table below presents the statistics of agreement for the alarm off sensor performance. A mean (median) absolute difference of 19.1% (15.3%), a correlation of 0.87 and a regression equation of 11.97 + (X) 0.81 were observed.

Sensor Performance, Alarm Turned Off

Numerical Agreement	
Mean Absolute Difference ± SD	19.1±16.1
Median Absolute Difference	15.3
Mean Numerical Bias ± SD	-16.9 ± 33.3
Median Numerical Bias	-14.00
Correlation	0.87
Slope	0.81
Intercept	11.97

The Bland Altman analysis yielded an average bias of -18.96 mg/dL with lower and upper 95% distribution limits of -82.2 and 48.4 mg/dL.

The Clarke Error Grid analysis indicates that 194 pairs (62.4%) fall in Zone A, 110 pairs (35.4%) fall in Zone B, 1 pair (0.3%) falls in Zone C, 6 pairs (1.9%) fall into Zone D, and 0 pairs (0.0%) fall into Zone E.

The sensitivity for hypoglycemia detection set at 70 mg/dL was 77% (17 out of 22), specificity 93% (268 out of 289), rate of false negatives was 23% (5 out of 22), and rate of false positives 55% (21 out of 289).

The sensitivity for hyperglycemic detection set at 250 mg/dL was 43% (13 out of 30), specificity 99% (279 out of 281), rate of false negatives was 57% (17 out of 30) and rate of false positives 13% (2 out of 15).

B. Sensor Performance with Hypoglycemic and Hyperglycemic Alarm Turned On (N= 29 sensors)

During Week 2 of the study, subjects wore sensors with the hypo- and hyperglycemic alarms turned on. A total of 29 sensors were evaluated with alarms turned on. A total of 392 meter blood glucose values were paired with a sensor value.

The table below presents the statistics of agreement for the alarm on sensor performance. A mean (median) absolute difference of 18.1% (14.7%), a correlation of 0.90 and a regression equation of 9.44 + (X) 0.84 were observed.

Sensor Performance, Alarm Turned Off

Numerical Agreement

Mean Absolute Difference ± SD	18.1±17.0
Median Absolute Difference	14.7
Mean Numerical Bias ± SD	-11.64
Median Numerical Bias	-14.8 ± 33.7
Correlation	0.90
Slope	0.84
Intercept	9.4

The Bland Altman analysis yielded an average bias of -14.8 mg/dL with lower and upper 95% distribution limits of -80.9 and 51.3 mg/dL.

The Clarke Error Grid analysis indicates that 259 pairs (66.1%) fall in Zone A, 126 pairs (32.1%) fall in Zone B, 1 pair (0.3%) falls in Zone C, 6 pairs (1.5%) fall into Zone D, and 0 pairs (0.0%) fall into Zone E.

The sensitivity for hypoglycemia detection set at 70 mg/dL was 78% (35 out of 45), specificity 88% (304 out of 347), rate of false negatives was 22% (10 out of 45), and rate of false positives 55% (43 out of 347).

The sensitivity for hyperglycemic detection set at 250 mg/dL was 67% (34 out of 51), specificity 99% (338 out of 341), rate of false negatives was 33% (17 out of 51) and rate of false positives 8% (3 out of 341).

C. Comparison of Sensor Performance (Alarms Off vs. Alarms On)

	Week 1 Sensors (Alarms Off) (n=32 sensors, 311 pairs)	Week 2 Sensors (Alarms On) (n=29 sensors, 392 pairs)	Comparison of Week 1 and Week 2 P-value
Numerical Agreement			
Mean Absolute Difference ± SD	19.1±16.1	18.1 ± 17.0	0.41
Median Absolute Difference	15.3	14.7	0.37
Mean Numerical Bias± SO	-16.9 ± 33.3	-14.8 ± 33.7	0.41
Median Numerical Bias	-14.0	-11.6	0.28
Correlation	0.87	0.90	0.03
Slope	0.81	0.84	0.12
Intercept	11.97	9.44	
Hypoglycemia Detection (<=70)			
Sensitivity	17/22 (77%)	35/45 (78%)	0.99
Specificity	268/289 (93%)	304/347 (88%)	0.04
False Negatives	5/22 (23%)	10/45 (22%)	0.99
False Alarms	21/38 (55%)	43/78 (55%)	0.99
Hyperglycemia Detection (>=250)			
Sensitivity	13/30 (43%)	34/51 (67%)	0.06
Specificity	279/281 (99%)	338/341 (99%)	0.99
False Negatives	17/30 (57%)	17/51 (33%)	0.06
False Alarms	2/15 (13%)	3/37 (8%)	0.62

In the above table, the following statistical tests were used: Independent T-test used to compare mean absolute percent difference and mean numerical bias; Wilcoxon Rank Sum Test used to compare median absolute percent difference and median numerical bias; Fisher's Z-test to compare correlation coefficients; Independent T-test to compare average slopes; Fisher's Exact Test to compare proportions.

D. Overall Sensor Performance (N= 61 sensors)

In order to provide for maximal statistical power, a combined analysis of Alarm Off and Alarm On periods was performed. This evaluation included all 61 sensors and all 703 paired blood glucose meter-glucose sensor data points.

The table below presents the statistics of agreement for overall sensor performance. A mean (median) absolute difference of 18.5% (14.9%), a correlation of 0.89 and a regression equation of 10.05 + (X) 0.83 were observed.

Sensor Performance, Alarm Turned Off

Numerical Agreement

Mean Absolute Difference ± SD	18.5±16.6
Median Absolute Difference	14.9
Mean Numerical Bias ± SD	-15.8 ± 33.5
Median Numerical Bias	-12.93
Correlation	0.89
Slope	0.83
Intercept	10.05

The sensitivity for hypoglycemia detection set at 70 mg/dL was 78% (52 out of 67), specificity 90% (572 out of 636), rate of false negatives was 22% (15 out of 67), and rate of false positives 55% (64 out of 636).

Receiver Operator Characteristic Curve analysis for optimal alarm threshold for hypoglycemic detection when the meter blood glucose is 70 mg/dL shows area under the curve is 0.935. The optimal hypoglycemic alarm threshold (i.e. the value that maximizes both sensitivity and specificity) was 75 mg/dL.

Sensor Glucose (mg/dL)	Sensitivity	Specificity
50	32.8%	1.4%
55	43.3%	2.7%
60	55.2%	3.9%
65	67.2%	6.8%
70	77.6%	10.1%
75	**85.1%**	**15.4%**
80	92.5%	18.2%
85	94.0%	20.9%
90	94.0%	23.9%

The sensitivity for hyperglycemic detection set at 250 mg/dL was 58% (47 out of 81), specificity 99% (617 out of 622), rate of false negatives was 42% (34 out of 81) and rate of false positives 10% (5 out of 622).

Receiver Operator Characteristic Curve analysis for optimal alarm threshold for hyperglycemic detection when the meter blood glucose is 250 mg/dL shows area under the curve is 0.966. The optimal hypoglycemic alarm threshold (i.e. the value that maximizes both sensitivity and specificity) was 195 mg/dL.

Sensor Glucose (mg/dL)	Sensitivity	Specificity
270	39.5%	0.2%
265	43.2%	0.3%
260	50.6%	0.5%
255	53.1%	0.6%
250	58.0%	0.8%
245	64.2%	1.0%
240	65.4%	1.5%
235	70.4%	1.9%
230	72.8%	2.6%
225	76.5%	3.5%
220	80.3%	4.7%
215	82.7%	5.6%
210	85.2%	6.8%
205	87.7%	7.6%
200	88.9%	8.5%
195	**91.4%**	**9.8%**
190	91.4%	10.6%

E. Agreement Between Sensor and Meter Based on Glycemic Categories

Because blood glucose meter values are known to have some degree of error, an alternative analysis of ordinal, or categorical agreement was performed. Both sensor and meter values of each of the 703 pairs were stratified into one of three glycemic categories: less than or equal to 70 mg/dL (hypo- alarm setting), 71-249 mg/dL, and greater than or equal to 250 mg/dL (hyper- alarm setting).

For 585 (83%) of the 703 pairs, the sensor and meter category were identical. For an additional 118 (17%), the meter and sensor fell into adjacent categories. For no pairs did the sensor category indicate an extreme glucose excursion (hypo- or hyperglycemia) in one direction and the meter in the opposite direction.

F. Potential Factors Influencing TGMS Performance

In order to identify possible mitigating factors in TGMS performance, the endpoints were stratified by blood glucose meter range and time of day.

	Meter Blood Glucose Range			
	<80	81-140	141-240	>240
Numerical Agreement				
Mean Absolute Difference ± SD	21.4 ± 26.1	20.4 ± 15.9	16.8 ± 13.3	15.4±11.6
Median Absolute Difference	11.9	17.8	13.6	12.4
Mean Numerical Bias ± SD	0.6 ± 23.0	-9.8 ± 26.5	-20.3 ± 33.7	-36.9 ± 44.5
Median Numerical Bias	-1.8	-11.1	-18.5	-32.7
Correlation	NA	NA	NA	NA
Slope	0.78	0.77	0.74	0.75
Intercept	14.46	14.79	25.77	37.3

	Sensor Time of Day			
	10pm to 3:59am (n=108 pairs)	4amto 9:59am (n=159 pairs)	10am to 3:59pm (n=229 pairs)	4pmto 9:59pm (n-207 pairs)
Numerical Agreement				
Mean Absolute Difference ± SD	19.7 ± 15.0	17.8 ± 21.6	18.9 ± 14.4	18.1 ± 15.2
Median Absolute Difference	17.8	12.0	15.1	15.0
Mean Numerical Bias ± SD	-19.6 ± 34.3	-10.0 ± 35.5	-194 ± 33.7	-14.1 ± 30.6
Median Numerical Bias	-17.0	-7.9	-15.0	-10.4
Correlation	NA	NA	NA	NA
Slope	0.83	0.88	0.81	0.77
Intercept	7.83	10.24	8.88	17.84

2. Multi-center Evaluation of the Accuracy and Alert Function of the Medtronic MiniMed TGMS in Subjects with Type 1 diabetes Mellitus, Clinical Report GS031

A two-period, randomized, multi-center study was conducted at 6 sites to demonstrate that the TGMS accurately depicts subjects' glucose levels when compared to periodic measurements obtained from a standard home blood glucose meter and to evaluate the sensitivity and specificity of the high and low glucose alert functions of the TGMS. A total of 71 subjects with Type 1 diabetes, aged 18-65 years, were randomized into either an Alert Group (35 subjects) or a Control Group (36 subjects). Each subject wore 4 sensors consecutively, for a period of 72 hours each.

Accuracy was evaluated on all paired data from both groups for both periods by absolute relative error (ARE), mean numerical bias, correlation, linear regression, Clarke Error Grid analysis and Bland-Altman measure of agreement. Sensitivity and specificity were calculated to assess agreement of the TGMA and blood glucose meter values above and below the alert thresholds. Efficacy was then evaluated with a within-subject design with control, comparing the differences from Period 1 and Period 2 between the two groups. A total of 4,453 sensor-meter data pairs were used to evaluate TGMS performance.

Results

A. Numerical Accuracy, by Treatment Group and Study Period

The absolute relative error (ARE), stratified by randomization group and study period is presented in the table below. A two-way analysis of variance was performed to test for differences in mean ARE, with randomization group and study period as factors. The main effect for Study Group was not statistically significant (p=0.65), while that for Study Period was statistically significant (p=0.008). A statistically significant interaction between randomization group and study period was found (p=0.02). For the Alert Group, there was no significant difference in the mean ARE between Period 1 and 2 (21.3 vs. 21.1, p=0.80). For the Control Group, the mean ARE was higher in Period 1 compared to Period 2 (22.9 vs. 20.1, p=0.0008).

	Alert Group		Control Group	
	Period 1	Period 2	Period 1	Period 2
Number of Paired Readings	1140	1217	1005	1091
ARE: Mean ± SD	21.3 ± 19.5 (17.8)	21.1 ± 18.0 (17.5)	22.9* ± 19.6 (18.5)	20.1*± 18.2 (15.5)

• Independent p-test, p=0.0008

The number/total of paired sensor readings in agreement with the comparative glucose reading, stratified by randomization group and study period is presented in the tables below. Agreement was defined as within ± 20 % for comparative readings greater than 80 mg/dL and within ± 20 mg/dL for comparative glucose readings less than or equal to 80 mg/dL.

Comparative Glucose, mg/dL	Total	Alert Group Period 1	Alert Group Period 2	Control Group Period 1	Control Group Period 2
40-80"	654/897 (73%)	184/239 (77%)	202/270 (75%)	121/187 (65%)	147 /201 (73%)
81-120	540/976 (55%)	150/268 (56%)	134/273 (49%)	121/218 (56%)	135/217 (62%)
121-240	1061/1812 (59%)	268/477 (56%)	238/426 (56%)	241/433 (56%)	314/476 (66%)
>240	467/768 (61%)	87/156 (56%)	170/248 (69%)	91/167 (54%)	119/197 (60%)
Overall	2722/4453 (61%)	689/1140 (60%)	744/1217 (61%)	574/1005 (57%)	715/1091 (66%)

In the table below, agreement was defined as within ± 30 % for comparative readings greater than 80 mg/dL and within ± 20 mg/dL for comparative glucose readings less than or equal to 80 mg/dL

Comparative Glucose, mg/dL	Total	Alert Group Period 1	Alert Group Period 2	Control Group Period 1	Control Group Period 2
40-80"	654/897 (73%)	184/239 (77%)	202/270 (75%)	121/187 (65%)	147 /201 (73%)
81-120	729/976 (75%)	199/268 (74%)	192/273 (70%)	166/218 (76%)	172/217 (79%)
121-240	1411/1812 (78%)	364/477 (76%)	321/426 (75%)	322/433 (74%)	404/476 (85%)
>240	610/768 (79%)	124/156 (79%)	210/248 (85%)	123/167 (74%)	153/197 (78%)
Overall	3404/4453 (76%)	871/1140 (76%)	925/1217 (76%)	732/1005 (73%)	876/1091 (80%)

B. Numerical Accuracy, Overall

The overall numerical accuracy for the 4,453 paired readings is presented in the table below.

	Overall
Number of Paired Readings	4453
ARE: Mean ±SD	21.3 ± 18.8
(Median)	(17.3)
Numerical Bias*: Mean ±SD	-12.8 ± 43.9
(Median)	(-7.7)
Correlation	0.87
Slope	0.80
Intercept	19.31

The number of paired sensor readings in agreement with the comparative glucose reading is presented below.

Comparative glucose (mg/dL)	Total	Agreement to within: +20%*	+30%*
40-80*	897	654 (73%)	654 (73%)
81-120	976	540 (55%)	729 (75%)
121-240	1812	1061 (59%)	1411 (78%)
>240	768	467 (61%)	610 (79%)
Overall	4453	2722 (61%)	3404 (76%)

C. Bland Altman Analysis

The Bland Altman analysis yielded an average bias of -12.8 mg/dL with lower and upper 95% distribution limits of -98.8 and 73.2 mg/dL

D. Clarke Error Grid Analysis

The Clarke Error Grid analysis indicated that 2662 pairs (59.8%) fell within Zone A, 1515 pairs (34%) fell within Zone B, 4177 pairs (93.8%) fell within Zones A and B, 16 pairs (0.4%) fell within Zone C, 250 pairs (5.6%) fell within Zone D, and 10 pairs (0.2%) fell within Zone E.

The number (%) of paired sensor readings in CEG zones, stratified by comparative glucose range, is presented in the table below.

Comparative glucose (mg/dL)	Clarke Error Grid Zones						
	Total	A+B	A	B	C	D	E
40-80*	897	724	594	130	0	171	2
	(20.1%)	(80.7%)	(66.2%)	(14.5%)	(0%)	(19.1%)	(0.2%)
81-120	976	976	540	436	0	0	0
	(21.9%)	(100%)	(55.3%)	(44.7%)	(0%)	(0%)	(0%)
121-240	1812	1796	1061	735	10	0	6
	(40.7%)	(99.1%)	(58.5%)	(40.6%)	(0.6%)	(0%)	(0.3%)
>240	768	681	467	214	6	79	2
	(17.2%)	(88.7%)	(60.8%)	(27.9%)	(0.8%)	(10.3%)	(0.3%)
Overall	4453	4177	2662	1515	16	250	10
	(100%)	(93.8%)	(59.8%)	(34.0%)	(0.4%)	(5.6%)	(0.2%)

E. Agreement by Glycemic Categories

An alternative analysis of categorical agreement was performed. Both the sensor and comparative meter blood glucose readings were stratified into one of four glycemic categories: 40 to 80 mg/dL, 81 to 120 mg/dL, 121 to 140 mg/dL, and greater than 240 mg/dL. The table below presents a cross tabulation of the sensor and meter glycemic categories. Of the 4453 paired readings, 2963 (67%) sensor readings were in agreement with the meter glycemic category.

Comparative glucose (mg/dL)	**Total**	**Sensor Glucose, mg/dL**			
		40-80	**81-120**	**121-240**	**>240**
40-80	897	699 (78%)	184 (21%)	14 (1%)	0 (0%)
81-120	976	302 (31%)	509 (52%)	165 (17%)	0 (0%)
121-240	1812	96 (5%)	349 (19%)	1261 (70%)	106 (6%)
>240	768	4 (1%)	11 (1%)	259 (34%)	494 (64%)

F. Alert Settings for Hypoglycemia Detection

To evaluate the low alert settings, the low alert threshold was set at 70 mg/dL. Of the 646 comparative glucose readings at or below 70 mg/dL, 431 (67%) were confirmed by the sensor (sensitivity) and 215 (33%) were not confirmed by the sensor (false negatives). For the 215 false negatives, the median sensor reading was 81 mg/dL (range from 70-207 mg/dL).

Of the 3807 comparative readings above 70 mg/dL, 3432 (90%) were confirmed by the sensor (specificity. Of the 806 sensor readings at or below 70 mg/dL, 375 (47%) were not confirmed by the comparative glucose meter (false positives). For the 375 false positives, the median comparative glucose reading was 87 mg/dL (range from 71 to 249 mg/dL).

Receiver Operator Characteristic Curve analysis for overall hypoglycemic detection ability of the TGMS shows area under the curve of 0.91. The optimal low alert threshold was found to be 82 mg/dL.

Sensor Low Alert Threshold (mg/dL)	Comparative glucose readings ≤70 mg/dL confirmed by sensor (Sensitivity)	Comparative glucose readings >70 mg/dL confirmed by sensor (Specificity)	Sensor readings ≤70 mg/dL not confirmed by comparative glucose readings (False Alerts)
60	42%	95%	41%
65	56%	92%	45%
70	67%	90%	47%
75	75%	88%	49%
80	83%	86%	51%
82	**84%**	**84%**	**52%**
85	87%	83%	54%
90	91%	80%	57%

G. Alert Settings for Hyperglycemia Detection

To evaluate the high alert settings, the threshold was set at 250 mg/dL. Of the 691 comparative glucose readings at or above 250 mg/dL, 435 (63%) were confirmed by the sensor (sensitivity) and 256 (37%) were not confirmed by the sensor (false negatives). For the 256 false negatives, the median sensor reading was 208 mg/dL (range 73-250 mg/dL).

Of the 3762 comparative readings below 250 mg/dL, 3663 (97%) were confirmed by the sensor (specificity. Of the 534 sensor readings at or above 250 mg/dL, 99 (19%) were not confirmed by the comparative glucose meter (false positives). For the 99 false positives, the median comparative glucose reading was 225 mg/dL (range 145 to 248 mg/dL).

Receiver Operator Characteristic Curve analysis for overall hyperglycemic detection ability of the TGMS shows area under the curve of 0.945. The optimal low alert threshold was found to be 192 mg/dL.

Sensor High Alert Threshold (mg/dL)	Comparative glucose readings ≥250 mg/dL confirmed by sensor (Sensitivity)	Comparative glucose readings <250mg/dL confirmed by sensor (Specificity)	Sensor readings ≥250 mg/dL not confirmed by comparative glucose readings (False Alerts)
190	88%	87%	44%
192	**87%**	**87%**	**43%**
200	85%	90%	40%
210	81%	92%	36%
220	77%	94%	31%
230	73%	95%	28%
240	68%	96%	22%
250	63%	97%	19%

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The results of preclinical qualification/validation testing and clinical trials to assess the performance of the TGMS system and alert functions using a real-time calibration algorithm establish reasonable assurance that this system is safe and effective for its intended use when utilized in accordance with the product labeling.

XIII. CDRH DECISION

CDRH issued an approval order on January 7, 2004. The final conditions of approval are cited in the approval order

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.