SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Continuous Subcutaneous Glucose Monitoring System
Device Trade Name:	Guardian RT
Applicant's Name and Address:	Medtronic MiniMed 18000 Devonshire Street Northridge, California 91325
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P980022/S011
Date of Notice of Approval to Applicant:	July 18, 2005

II. INDICATIONS FOR USE

The Guardian RT is indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin in adults (ages 18 and older) with diabetes mellitus for the purpose of improving diabetes management. It alerts if a glucose level falls below or rises above preset values. Values are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on Guardian values.

Guardian RT provides real-time glucose values that allow users to track patterns in glucose concentrations and to possibly identify episodes of low and high blood glucose episodes. It also stores the data so that it can be analyzed to track patterns. Glucose data can be further downloaded to PC software for analysis of historical glucose values.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Guardian RT labeling.

DEXCOM EXHIBIT 1059
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V. DEVICE DESCRIPTION

The Medtronic MiniMed MMT-7900 Guardian® RT (Real Time) System consists of a Monitor (MMT-7901), which records and displays real time glucose values calculated based on information received from a transmitter (MMT-7700) and a Glucose Sensor (MMT-7002). The Guardian RT system uses a modified version of the MMT-7002 glucose sensor approved on June 15, 1999 under PMA P980022. The Guardian RT MMT-7901 monitor stores up to 21 days of data that can be downloaded to a computer using the Medtronic MiniMed Com-Station (MMT-7301) and the Medtronic MiniMed Guardian Solutions Software (MMT-7315).

The model MMT-7700 transmitter, the MMT-7301 Com-Station and the MMT-7315 Solutions software have all been previously approved by FDA under P980022 or subsequent PMA supplements and therefore the only new devices approved under this PMA supplement are the MMT-7901 monitor and the modified version of the MMT-7002 sensor.

The hardware of the MMT-7901 Guardian RT monitor is identical to that of the MMT-7600 monitor approved under P980022/S010. The Guardian RT monitor uses new software that allows the display of calculated glucose concentrations on the monitor in real-time. The algorithm used to convert sensor signals to glucose concentrations has also been modified to improve accuracy.

The system requires calibration using a fingerstick glucose measurement at least every 12 hours and users are instructed to perform confirmatory fingerstick measurements before making therapy adjustments in response to the displayed values.

Description of System Components

1. Glucose Sensor (MMT-7002)

A modified MMT-7002 Glucose Sensor (original sensor approved in June 1999 under P980022) is used with the Guardian RT system. The modified sensor version does not include the outer hydrophilic membrane that is utilized in the currently approved version of the MMT-7002 but is identical in all other respects.

2. Guardian Transmitter (MMT-7700)

The MMT-7700 transmitter used as part of the Guardian RT system is the same device use with the Guardian system and was previously approved by FDA under P980022/S010. The model MMT-7700 Transmitter consists of a small, teardrop shaped plastic case, housing a battery pack and two printed circuit board assemblies. A short cable (approximately three inches) extends from one end of the case and terminates in a connector that mates with the MMT-7002 glucose sensor. Connecting the sensor to the transmitter closes a switch, which connects three 1.5-

volt silver oxide cells to the printed circuit boards and activates the transmitter. These cells are non-replaceable and are intended to last the life of the unit, which is approximately one year under normal use condition. The MMT-7700 transmitter reads and processes information and transmits a filtered sensor reading via radio frequency (RF) communication to the monitor every 5 minutes. It is attached to the body by means of an adhesive patch nearby the inserted sensor.

3. Guardian® RT Monitor (MMT-7901)

The MMT-7901 Guardian RT monitor is identical to the Guardian MMT-7600 monitor previously approved by FDA under P980022/S010 except for the software program used to process and display glucose information transmitted from the MMT-7700 transmitter. The Guardian RT monitor uses new software that allows the display of calculated glucose concentrations on the monitor in real-time. The algorithm used to convert sensor signals to glucose concentrations has also been modified to improve accuracy.

The monitor acts as the primary system interface with the user. It contains an LCD display and 5 buttons for operation. The Monitor displays date and time information, and sensor glucose values that are updated automatically. It allows user entry of BG calibration values, and entry of event markers with associated values that are useful for interpretation of downloaded data.

The user can program various setup options for personalization. The user can select high and low glucose alarm threshold settings and alarm repeat intervals as appropriate for their conditions. Alarms can be set to signal by audio or vibrate mode or both. Glucose values can be displayed in either mg/dL or mmol/L units, and time of day can be displayed in either 12 hour or 24-hour format. The Guardian RT monitor offers language selection for user interface display. Two replaceable AAA disposable alkaline batteries power the monitor. New batteries will function in excess of one month of continuous operation.

The monitor holds up to 21 days of sensor data and other information in memory. Once the memory is full, existing information is overwritten on a first in, first out basis. The information stored in the monitor can be downloaded to the PC using the MMT-7315 software for viewing glucose trends from the most recent 21 days of monitor operation.

4. Com-Station (MMT-7301)

The Com-Station (originally approved under P980022) is connected to the PC via a serial cable and commanded by the PC software program to communicate with Guardian RT monitor to download information from the monitor's memory. The Com-Station acts as a conduit that passes information from the Monitor to the PC. It mates with the shape of the Monitor to align the IR communication ports between the two devices. The Com-Station plugs into an AC power outlet and uses a power transformation cable for DC conversion of the input power.

5. Guardian Solutions PC Software (MMT-7315)

The MMT-7315 Guardian Solutions PC software (originally approved under P980022/S010) is used to download and display information stored in the Guardian RT monitor. The data from each individual download session is stored in separate files on the user's PC. Glucose data is displayed in graphs and charts for user review of glucose patterns and trends. Reports can be printed, saved and reopened for later review.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Periodic self-glucose monitoring using home glucose meters will provide information regarding variations in glucose levels. Additionally, adult patients may use the Guardian system approved under P980022/S010 to record continuous interstitial glucose information and provide real-time hypoglycemia and hyperglycemia alerts.

VII. MARKETING HISTORY

The Guardian RT system has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICES ON HEALTH

Inaccurate glucose values or inappropriate alarms provided by the *Guardian RT* could result in inappropriate administration of insulin or ingestion of carbohydrates. Such inappropriate treatment decisions could result in exacerbation of the symptoms associated with hypoglycemia and hyperglycemia.

IX. SUMMARY OF PRECLINICAL STUDIES

System Level Functional Testing

Operation of the Guardian RT system at the system level was evaluated by exercising the major functions of the system and confirming that the system operated in accordance with specified performance requirements. In addition, system level simulated use testing was performed by recording data from three Guardian systems over a three-day period. During this period, the sensors were periodically transferred to solutions with various glucose concentrations to simulated changes in a patient's glucose levels. All specified acceptance criterion were met during this testing.

Environmental Qualification

The Guardian RT system was not subjected to environmental and EMC testing since all hardware is identical to that used in the previously approved Guardian system (P980022/S010) and therefore the testing previously performed for the Guardian system is also applicable to the Guardian RT system.

Modified MMT-7002 Glucose Sensor

The version of the MMT-7002 sensor used with the Guardian RT system is identical to currently marketed MMT-7002 sensor with the exception that the outer hydrophilic membrane has been removed. Extensive qualification testing conducted for the modified sensor was performed and confirmed that all aspects of performance for this new version were the same as or superior to those of the current marketed sensor.

Software Validation (MMT-7901 Monitor)

Extensive verification and validation testing was conducted to confirm that the software used in the MMT-7901 monitor performed in accordance with established specifications. This testing confirmed that all major requirements were met. All identified deviations from desired or expected operation were carefully reviewed and determined to have no significant impact on the safe and effective use of the device.

X. SUMMARY OF CLINICAL STUDIES

In-House Evaluation of Modified MMT-7002 Sensor

An in-house study was conducted to provide a preliminary assessment of the performance of the modified version of the MMT-7002 sensor (without the outer hydrophilic membrane) used with the Guardian RT system. Medtronic MiniMed employees who volunteered to participate in this study wore the modified version of the MMT-7002 sensor for up to 72 hours. During this period, the raw current signals from the sensor were continuously recorded. Subjects also performed frequent finger stick glucose measurements during their participation in the study.

The algorithm used in the Guardian RT monitor to convert sensor signals to glucose concentrations was retrospectively applied to the data collected. Finger stick glucose measurements taken by the subjects during the study were used as calibration values and reference values for the purpose of assessing sensor accuracy. For comparison purposes, the Guardian RT algorithm was also applied retrospectively to raw sensor current values collected during a previously clinical trial that utilized the original version of the model MMT-7002 sensor.

Results

Sensor performance for the modified and original versions of the MMT-7002 sensor was calculated for the following five variables: Ratio of Calibration Errors to Calibration points (Calibration Error Ratio), Median Sensor Life (hours), Mean Absolute Difference (%), Correlation Coefficients, and Clark Error Grid Analysis. These results are summarized in the table that follows.

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Sensor Version	eval. points	cal. points	cal. errors	cal. error ratio	sensor life in hours (median)	MAD %	CC	Clark Error Grid % (A+B)
MMT-7002 (modified)	557	668	13	1.94%	70.20	17.32	0.89	98.44
MMT-7002 (original)	2919	3460	165	4.77%	67.08	21.2	0.86	93.7

The results show a decrease in Calibration Error Ratio, increase in median sensor lifetime, decrease in Mean Average Deviation, increase in Correlation, and increase in the percentage of points within the Clarke Error Grid A/B regions, when comparing the modified sensor to the current production sensor.

Conclusions:

A preliminary in-house evaluation confirmed improvements in all measures of performance when the Guardian RT algorithm was applied to data collected with the modified version of the MMT-7002 (without the other hydrophilic membrane) compared to results when the Guardian RT algorithm was applied to data previously collected with the original version of the MMT-7002 sensor.

Performance Evaluation Of the Medtronic MiniMed Telemetered Glucose Monitoring System II (TGMS II) in Subjects with Type 1 Diabetes Mellitus

Methods

This study was conducted at one investigational site and involved a total of 16 subjects with Type 1 Diabetes Mellitus. Each subject wore two MMT-7002 sensors (modified version without outer hydrophilic membrane) simultaneously. Each sensor was connected to a MMT-7700 transmitter. Subjects also wore prototype version MMT-7901 monitors to record sensor signals every five minutes.

Venous blood samples were drawn every 30 minutes and glucose concentrations were measured using a YSI STAT Plus Glucose Analyzer. Subjects were also asked to perform capillary glucose measurements using a BD Logic Blood Glucose Monitor seven times per day during the study

Results

The accuracy of the Guardian RT system was assessed by retrospectively applying the algorithm used in the MMT-7901 Guardian RT monitor to the data collected during the study. Development of this algorithm was completed before the study was initiated and therefore the dataset used to develop the algorithm was completely separate from and independent of the dataset used to assess the

accuracy of the Guardian RT system. Performance statistics were calculated both using YSI measurements as calibration values and the BD Logic Glucose Monitor measurements as calibration values. The dataset from this study consisted of a total of 3941 paired YSI reference values and corresponding Guardian RT glucose concentrations when the BD Logic measurements were used as calibration values and 4067 paired YSI reference values and corresponding Guardian RT glucose concentrations when the YSI measurements were used as calibration values

The mean and median ARE (Absolute Relative Error) between the glucose concentration calculated by the Guardian RT and the corresponding YSI Analyzer reference value were 17.24% and 13.98% respectively when YSI measurements were used as calibration values and 19.67% and 15.55% respectively when the BD Logic capillary glucose measurements were used as calibration values. On average, the Guardian RT glucose values were 12.0 mg/dL less than the YSI Analyzer reading when the YSI Analyzer measurements were used for calibration and 15.0 mg/dL less than the YSI Analyzer reading when the BD Logic measurements were used for calibration.

Overall, when the BD Logic measurements were used as calibration values, 62% of the Guardian RT readings were within 20% of the reference YSI values and 79% of the readings were within 30%. When the YSI Analyzer measurements were used as calibration values, 69% of the Guardian RT readings were within 20% of the reference YSI values and 83% of the readings were within 30%.

The following table shows the percent of Guardian RT readings within 20% and 30% of the YSI values (or within 20 mg/dL for values < 80 mg/dL), broken down into various glucose ranges.

Plasma Glucose Range (mg/dl)	**Percent Within 20%**	**Percent Within 30%**
40-80*	68%	68%
>80-120	60%	77%
>120-240	62%	81%
>240	61%	82%

**For the Low glucose range, 40-80 mg/dl (2.2-4.4 mmol/l), the value shown is the percent within 20 mg/dl (1.1 mmol/l).*

When the BD Logic capillary glucose measurements were used as calibration values, the Clarke error grid analysis indicated that 96.0% of Guardian RT glucose values were in the clinically acceptable Zones A and B. When the YSI Analyzer measurements were used as calibration values, 95.8% of values were in the clinically acceptable Zones A and B.

The following table shows the percentage of points falling within each zone, stratified according to the range of glucose concentrations.

Glucose Range (mg/dl)	Number and (%) of Data Points Evaluated	A+B	A	B	C	D	E
40-80	356 (9)	271 (76.1)	214 (60.1)	57 (16.0)	2 (0.6)	80 (22.5)	3 (0.8)
81-120	769 (20)	768 (99.9)	463 (60.2)	305 (39.7)	1 (0.1)	N/A*	N/A
121-240	2362 (60)	2352 (99.6)	1476 (62.5)	876 (37.1)	4 (0.2)	N/A	6 (0.2)
>240	454 (11)	394 (86.8)	277 (61.0)	117 (25.8)	N/A	59 (13.0)	1 (0.2)
Overall	3941 (100)	3785 (96.0)	2430 (61.7)	1355 (34.4)	7 (0.2)	139 (3.5)	10 (0.2)

**N/A means that the Clarke Error Grid does not consider the possibility of these zones in that concentration range*

When the BD Logic glucose measurements were used as calibration values, the Guardian RT system identified glucose values ≤70 mg/dL with 49% sensitivity, 96% specificity, and 60% false alerts. The Guardian RT system showed a similar ability to detect glucose values ≥250 mg/dL with 53% sensitivity, 98% specificity, and 25% false alerts. ROC curve analysis indicated optimal detection of hypoglycemia was achieved with the alert set at 93 mg/dL (85% sensitivity, 85% specificity, and 77% false alerts), and optimal detection of hyperglycemia was achieved with the alert set at 190 mg/dL (85% sensitivity, 85% specificity, and 64% false alerts).

When the YSI Analyzer measurements were used as calibration values, the Guardian RT system identified glucose values ≤70 mg/dL with 43% sensitivity, 97% specificity, and 61% false alerts. The Guardian RT system showed a similar ability to detect glucose values ≥250 mg/dL with 54% sensitivity, 99% specificity, and 21% false alerts. ROC curve analysis indicated optimal detection of hypoglycemia was achieved with the alert set at 95 mg/dL (86% sensitivity, 86% specificity, and 76% false alerts), and optimal detection of hyperglycemia was achieved with the alert set at 195 mg/dL (87% sensitivity, 86% specificity, and 61% false alerts).

This study was also designed to look at the reproducibility of two Sensors worn simultaneously at different locations on the body. Precision was estimated by comparing the glucose readings from the two Guardian RT systems. In this study 11,475 paired Sensor Guardian RT values were obtained. On average, they were different by 17.2%.

Low and High Alerts

The ability of the Guardian RT to detect high and low glucose levels was measured in the same clinical study.

The Low Glucose Alert

The Low Glucose Alert was evaluated for its ability to detect glucose levels at 70 mg/dl or below using the YSI 2300 STAT Plus glucose analyzer. As a reference, with the Low Glucose Alert set at 70 mg/dl, 49% (100/205) of low glucose events were detected by the Guardian RT. Better detection of low blood glucose is obtained when the Low Glucose Alert level is set higher. For example, setting the Low Glucose Alert at 90 mg/dl instead of 70 mg/dl increases the ability to detect low blood glucose levels from 49% to 82% (see the table below).

When the Guardian RT Low Alert was set at 70 mg/dl, 43% of the results were considered false alerts (actual blood glucose values are greater than 85 mg/dl). The table below shows the percent of Low Glucose readings correctly identified by the Guardian RT for specific settings.

Guardian RT Low Alert Setting (mg/dl)	**True Alert Rate***	**False Alert Rate****
70	49%	60%
80	68%	64%
90	82%	75%
100	90%	79%

** True Alert Rates are the % of times when the glucose level was at or below the alert setting and the alert sounded.*

*** False Alerts Rates are the % of times when the Guardian RT Sensor alarmed but the blood glucose level was greater than the alert rate.*

The High Glucose Alert

The High Glucose Alert was evaluated for its ability to detect glucose levels at 250 mg/dl or above using the YSI analyzer. As a reference, with the High Glucose Alert set at 250 mg/dl, 53% (195/365) of high glucose events were detected by the Guardian RT. Better detection of high blood glucose can be obtained when the High Glucose Alert is set at a lower level. For example, setting the High Glucose Alert at 190 mg/dl instead of 250 mg/dl increases the ability to detect high blood glucose levels from 53% to 85% (see the table below).

When the Guardian RT High Alert was set at 250 mg/dl, 7.2% of the results were considered false alerts (actual blood glucose values are less than 225 mg/dl). The table below shows the percent of High Glucose readings correctly identified by the Guardian RT for specific settings.

Guardian RT High Alert Setting (mg/dl)	**True Alert Rate***	**False Alert Rate****
190	85%	64%
200	81%	58%
225	67%	40%
250	53%	25%

** True Alert Rates are the % of times when the glucose level was at or below the alert setting and the alert sounded.*

*** False Alerts Rates are the % of times when the Guardian RT Sensor alarmed but the blood glucose level was greater than the alert rate.*

Guardian RT Sensor Performance and Calibration Stability As a Function of Time

The Guardian RT Sensor may be worn for up to 3 days (72 hours) and must be calibrated at least twice a day. Two sets of data, approximately equal in number, were collected during the clinical trial. One data set was generated when the frequency of calibrations averaged 3.5 per day (Data Set A), and the other averaged 5 times a day (Data Set B). During the study, a total of 38 Sensors were evaluated in 16 individuals.

As per the stratified Clarke Error Grid analysis above , agreement between Guardian RT values and YSI values tends to be poorer at low and high glucose concentrations when compared to other concentration ranges.

Guardian RT performance in the hypoglycemic range, as a function of Sensor insertion time, is shown in the table below. Results from the two different data sets

are presented. The two populations were separated according to the number of calibrations per day. The table represents the percentage of Data Points in the 40-80 mg/dl range that fell within 20 mg/dl. Data is presented in 12-hour increments.

Data Set	0-12 hrs	12-24 hrs	24-36 hrs	36-48 hrs	48-60 hrs	60-72 hrs
A	78%	81%	73%	65%	56%	41%
B	67%	70%	93%	60%	75%	38%

An analysis of the mean percentage of Absolute Relative Error (ARE %) and standard deviations, across 12-hour increments of wear periods, appears in the table below. Both data sets are pooled together in this data.

Hours From Insertion	Mean ARE (%)	Std. Dev.
0-12 hrs	24.84	20.04
12-24 hrs	19.66	16.17
24-36 hrs	16.43	15.62
36-48 hrs	18.23	19.27
48-60 hrs	16.59	14.25
>60 hrs	22.95	23.51

The median Sensor life from Data Sets A and B were 57.5 hours and 72.9 hours, respectively. Twenty-one of the Sensors operated for 72 hours, while the others were removed for a variety of reasons, most often because of calibration errors.

The percentage of Guardian RT readings within 20 mg/dl and 30 mg/dl of YSI readings from 40-80 mg/dl, and the percentage of readings within 20% and 30% of YSI readings from 81-120 mg/dl, was analyzed according to time after Sensor insertion and according to the glucose-concentration range (as determined by the YSI analyzer). The data is in the following two tables.

	Percentage of Guardian RT values within 20 mg/dl of YSI laboratory readings		Percentage of Guardian RT values within 30 mg/dl of YSI laboratory readings	
Glucose Range (mg/dL)	**During first 60 hours of Sensor wear**	**After 60 hours of Sensor wear**	**During first 60 hours of Sensor wear**	**After 60 hours of Sensor wear**
40-80	62-82%	39%	78-91%	67%

	Percentage of Guardian RT values within 20% of YSI laboratory readings		Percentage of Guardian RT values within 30% of YSI laboratory readings	
Glucose Range (mg/dL)	**During first 60 hours of Sensor wear**	**After 60 hours of Sensor wear**	**During first 60 hours of Sensor wear**	**After 60 hours of Sensor wear**
81-120	57-66%	48%	72-84%	66%

Performance of the Guardian RT was evaluated according to the length of time since calibration. This data is not conclusive because of the limited number of data points during the final 3 hours of the 12hour calibration cycle, i.e., 10. In contrast, 3-hour time bins, earlier in the 12-hour cycle, contained hundreds of data points. This may suggest that calibrations are often required prior to the 12-hour calibration cycle.

Affects of Calibration Frequency

The average bias when Guardian RT was calibrated ~ 3.5 times a day was -20.5 + 41 mg/dl (lower limit -22.40 mg/dl and upper limit -18.63 mg/dl). In those calibrated ~ 5 times a day, the bias was -10.2 mg/dl + 36 mg/dl (lower limit -11.74 mg/dl and upper limit -8.66 mg/dl).

When comparing Guardian RT units that were calibrated less often to those calibrated more often, the following alarm performance was observed:

- Specificity increased 2-4% in the hypoglycemic range and decreased 0-2% in the hyperglycemic range
- Sensitivity increased between 5-9% across the hyperglycemic range, and decreased 7-16% when the alarm was set to 80 mg/dl or below, and decreased 3- 7% when set between 85 and 100 mg/dl

Stratified error grid analysis also shows better performance in the hypoglycemic range when fewer calibrations are performed, i.e., 62% of data points are in Zone A when fewer calibrations were performed, whereas 58% were in Zone A when more calibrations were performed.

XII. CONCLUSION DRAWN FROM THE STUDIES

The results of preclinical qualification/validation testing and clinical trials to assess the performance of the Guardian RT system with real-time availability of results establish reasonable assurance that this system is safe and effective for its intended use when utilized in accordance with the product labeling.

XII. PANEL RECOMMENDATIONS

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. FDA DECISION

FDA issued an approval order on July 18, 2005

XIV. APPROVAL SPECIFICATION

Directions for use: See labeling

Hazards to Health from use of Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events sections in the labeling

Post Approval Requirements and Restrictions: See approval order