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SUMMARY MINUTES OF THE

CLINICAL CHEMISTRY AND

CLINICAL TOXICOLOGY DEVICES PANEL MEETING

February 26, 1999

OPEN SESSION

**Gaithersburg Marriott
9751 Washingtonian Blvd.
Gaithersburg, Maryland**

Clinical Chemistry and Clinical Toxicology Devices Panel Meeting**February 26, 1999****Attendees****Chairperson****Henry Nipper, Ph.D.****Voting Members****Robert Rej, Ph.D.****Beverly Harrington-Falls, M.D.****Sherwood Lewis, Ph.D.****Martin Kroll, M.D.****Barbara Manno, Ph.D.****Temporary Voting Members****Steven Clement, M.D.****James Cooper, M.D.****Arlan Rosenbloom, M.D.****Janine Janosky, Ph.D.****James Everett, M.D.****Patient Representative****James Reed, B.S.E.****Consumer Representative****David Kruger, R.N.****Industry Representative****Robert Habig, Ph.D.****Executive Secretary****Sharon K. Lappalainen, M.T. (ASCP)****FDA****Steven I. Gutman, M.D., M.B.A.****Director, Division of Clinical Laboratory Devices****FDA**

OPENING REMARKS

Executive Secretary Sharon Lappalainen began the Open Session at 8:35 a.m. and introduced the topic of discussion, a premarket approval application (P980022) for MiniMed's continuous glucose monitoring system (CGMS) for the continuous recording of interstitial glucose levels in persons with diabetes mellitus. She noted that the PMA for the SalEst Test from Biex, Inc., discussed at the last panel meeting on December 10, 1997, had been granted approval to the market. Ms. Lappalainen welcomed Patient Representative James Reed, who would be representing diabetes patients on the day's panel. Ms. Lappalainen read the appointments to temporary voting membership for the panel and the conflict of interest statement, noting that matters concerning Drs. Kroll, Rifai, and Clement had been considered but their full participation allowed.

Dr. Steven Gutman, director of the FDA Division of Clinical Laboratory Devices, introduced the new Branch Chief of Clinical Chemistry and Clinical Toxicology, Dr. Jean Cooper. Dr. Gutman also presented a plaque to Dr. Robert Rej, who was completing his term on the panel, and thanked him for his work. Ms. Lappalainen then turned the meeting over to Dr. Nipper, who asked the panel participants to introduce themselves.

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Ms. Beth Silvers, R.D., L.D.N., C.D.E., a diabetes educator, president of MetroLina, and a diabetes patient with insulin pump experience, recommended approval of the device for insulin-dependent Type 1 pump wearers. She suggested that the device might also be useful for non-pump wearers and Type 2 patients after sufficient experience.

Kenneth Emancipator of the American Society for Clinical Pathologists

stated that the interstitial device should display the same level of precision and accuracy as any other blood glucose monitoring device but did not need to be equivalent to a laboratory device.

SPONSOR PRESENTATION

Dr. John Mastrototaro read the device indications for use, discussed the importance of continuous monitoring, and described the device, noting that the CGMS is intended to supplement finger stick measurements. He provided data from feasibility studies on 70 patients and sensor calibration calculations and discussed use of CGMS and sample patient data, concluding that the CGMS provides retrospective graphs of glycemic excursions facilitating therapy adjustments and that the regression calibration method is superior to the one-point calibration approach. Dr. Mastrototaro described a simulated patient study that evaluated CGMS in beakers of varying glucose concentration to simulate patient monitoring and concluded that feasibility studies and simulated patient studies demonstrate the utility of the CGMS to track glycemic excursions.

Dr. Jorge Mestman discussed clinical experience, including complications of diabetes mellitus, mortality data, and frequency of hypoglycemia. He discussed feasibility studies conducted at the University of Southern California and physician and patient experience and concluded that the CGMS was easy for patients to insert and use, did not introduce safety risks, and will provide clinicians with more data than are otherwise available.

Dr. Todd Gross discussed results of the multi-center clinical study, presenting study objectives, a protocol overview, safety and efficacy results, data on regression

calibration and CGMS performance, and safety and efficacy study conclusions, based on four study sites and 62 patients.

Dr. Alan Marcus discussed the clinical utility of standard blood glucose monitoring and potential benefits of continuous glucose monitoring. He described the CGMS implementation process and patient glucose profiles. Dr. Marcus concluded that conventional blood glucose monitoring is not adequate for assessing patients' glycemic control, but optimal self-monitoring of blood glucose guided by CGMS monitoring may decrease the risk of glucose excursions by providing trending information that targets times of poor glycemic control.

FDA PRESENTATION

Dr. Steven Gutman summarized the history of home glucose testing and the impact of minimally invasive or noninvasive techniques, noting the FDA's commitment to work with sponsors on devices to better manage diabetes. He noted that the submission under consideration was a first-of-a-kind device and was jointly reviewed by three FDA divisions, whose reviewers he introduced. Dr. Gutman read the indications for use and listed six points on device use concerning prescription and occasional rather than everyday use as a supplement to standard invasive glucose measurements and guiding future management of patients. He asked for input on how to understand and evaluate the performance of this technology, in particular in labeling. He noted that the device has been studied in a small population with a substantial data set, using several different means of data analysis.

John Dawson, Statistician in the Division of Biostatistics, expressed his agreement with providing a data summary to physicians to aid in interpreting trend data.

He focused on the sponsor's evaluation of data and raised statistical issues involving the loss of data to ambiguous zones and the possibility of biased information. Mr. Dawson suggested a different statistical evaluation scheme that was not inconsistent with the company's approach.

Gregory Campbell, Ph.D., Director of the Division of Biostatistics, discussed a range of statistical issues involved in the sponsor's data, including notation, assumptions, measurement error and attenuation of the slope, as well as other concerns.

Dr. Gutman read eight FDA questions to the panel for their consideration.

OPEN COMMITTEE DISCUSSION

Panel discussion involved a number of calibration issues and concerns. Dr. Gutman clarified that the FDA was not asking the panel to resolve calibration and statistical issues but to look at the product globally and decide if its effectiveness was sufficient for marketing approval, or if additional data should be gathered pre or post approval.

Other panel concerns involved patient demographics, in particular whether study data were sufficient to apply to use with African Americans, with Type 2 diabetic patients, with diabetic patients with other illnesses, with pediatric patients, or with women who are pregnant.

Panel Discussion of FDA Questions

The panel agreed unanimously that the data generated by the MiniMed Sensor provide useful information for the management of diabetes, and they approved of the trend of giving patients and physicians more data. Some reservations were expressed on calibration method and data and on applicability of the data to Type 2 diabetics, non-

Caucasian patients, and pregnant women. They recommended that some notation on the quality of the data should be added to the bottom of the data graphs included in the software.

The panel had some disagreement on whether successfully calibrated patients can be identified, with the majority agreeing that they could be, but with some qualifications on the need for broader ranges of patients, duration with disease, and types of diabetes and on the definition of successful calibration. Having some metric and printout to add value to the accuracy of the calibration was suggested, although one panel member suggested that it was the trend over time rather than exact calibration that was important.

The panel suggested additional data on a wider range of patient ages, duration of diabetes, type of diabetes, and patient demographics. They also suggested a small data set using serum glucose levels to calibrate the sensor or whole blood glucose on a YSI instrument superimposed with the algorithm.

On potentially confounding factors, the panel suggested that bilirubin and high triglycerides should be considered. Demographic data should be analyzed and stratified to look for confounding factors. Other interference factors such as patient drug regimens and new health events could be analyzed after the device is released.

The panel agreed that the product as currently configured, calibrated, and studied is likely to be an effective aid in the management of diabetes. Most wanted additional postmarket data as discussed above, but two wanted premarket data on use with Type 2 diabetics, non-Caucasians, and pregnant women, as well as evaluation of a limited number of patients with a YSI device. In general the panel thought the data presented

supported the claim that the sensor can be used for up to 72 hours for narrowly selected patients.

On labeling, the panel suggested that the nature of associations between interstitial and whole blood glucose values needs clarification and that the nature of its intermittent or occasional use should be underscored. The demographic limitations of the study data should be mentioned in the labeling. An educational pamphlet was suggested for clinicians and patients, with the patient education package rewritten by diabetes educators in simpler language with pictures. The patient education package should include a video, instructions for device cleaning, case studies, a section on “what ifs,” and a take-home booklet in user-friendly language. A section should be added on the importance of blood glucose monitoring and of the diabetes care team and on the benefits of better glucose control, noting that extreme fluctuations are typical for diabetics. One member noted a concern about non-diabetic specialists’ understanding of this device and its function

Sponsor Comments

The sponsor noted their concern about proper education of physicians in the use of this device and said they would incorporate the panel’s suggestions into their physician education program.

OPEN PUBLIC SESSION

Dr. Elaine Pass, a Type 1 diabetic and physician, stressed the importance of this device for helping the diabetic patient to achieve **glycemic** awareness and compliance.

Sponsor Remarks

The sponsor thanked the panel members and the FDA for their review.

VOTE AND RECOMMENDATIONS

Executive Secretary Sharon Lappalainen read the voting procedures and listed the voting members. A motion was made, seconded, and unanimously passed to recommend the PMA as approvable subject to the following conditions: (1) Data should be gathered on potential interferents such as, bilirubin, triglycerides, medications, etc. (2) Additional studies should be performed to gather data from use in Type 2 diabetics, patients of non-Caucasian racial backgrounds, children with diabetes, diabetics with concomitant disease states, and long- and short-term duration diabetics. (3) Validation of the proposed calibration should be done and calibration problems resolved. (4) Labeling changes should be made as suggested by the panel and the FDA, in addition to providing additional patient education information.

A motion was made, seconded, and unanimously agreed to recognize with gratitude Sharon Lappalainen for her work as Executive Secretary and to wish her well in her new position. It was noted that tentative future dates for panel meetings are September 23-24 and December 6, 1999. The meeting was adjourned at 5: 15 p.m.

I certify that I attended the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel on February 26, 1999, and that these minutes accurately reflect what transpired.



Veronica J. Calvin
Executive Secretary, FDA
For Former Executive Secretary Sharon Lappalainen, M.T. (ASCP)

I approve the minutes of this meeting as recorded in this summary.



Henry C. Nipper, Ph.D.
Chairperson