

SUMMARY MINUTES OF THE

CLINICAL CHEMISTRY AND

CLINICAL TOXICOLOGY DEVICES PANEL MEETING

October 28, 1999

OPEN SESSION

**9200 Corporate Boulevard
Conference Room 20 B
Rockville, Maryland**

Clinical Chemistry and Clinical Toxicology Devices Panel Meeting**October 28, 1999****Attendees****Chairperson****Henry C. Nipper, Ph.D.****Voting Members****Sherwood C. Lewis, Ph.D.****Barbara R. Manno, Ph.D.****Nader Rifai, Ph.D.****Arlan L. Rosenbloom, M.D.****Temporary Voting Members****Steven Clement, M.D.****Basil T. Doumas, Ph.D.****James Everett, M.D., Ph.D.****Janine E. Janosky, Ph.D.****Robert Rej, M.D.****Consumer Representative****David F. Kruger, M.S.N.****Industry Representative****Alton D. Floyd, Ph.D.****Guest****Mary M. Kimberly, Ph.D.****Guest Speaker****Henry N. Ginsberg, M.D.****Executive Secretary****Veronica J. Calvin, M.A.****FDA****Director, Division of Clinical Laboratory Devices****Steven I. Gutman, M.D., M.B.A.****FDA**

OPENING REMARKS

Panel Chairperson Dr. Henry Nipper began the Open Session at 9:10 a.m. Panel Executive Secretary Veronica Calvin introduced the topic of discussion, a premarket notification for an over-the-counter (OTC) device that measures triglycerides from whole blood fingersticks.

Ms. Calvin also summarized the February 26, 1999 panel meeting, at which the panel unanimously recommended approval of a premarket approval application (PMA) for MiniMed, Inc.'s Continuous Glucose Monitoring System, subject to the conditions of submission of additional data regarding interference, validation of the calibration algorithm, use in patient groups not previously studied, and labeling changes. The device was granted full approval on June 15, 1999.

Ms. Calvin introduced guests Dr. Henry Ginsberg and Dr. Mary Kimberly and Industry Representative Dr. Alton Floyd, who was substituting from another panel. She asked panel members to introduce themselves and read the conflict of interest statement, noting that matters concerning panel members Drs. Kroll, Rifai, Rosenbloom, Doumas, and Ms. Kruger and guest speaker Dr. Ginsberg had been considered but their full participation was allowed.

Dr. David Brown of the Office of Science and Technology gave the panel an update on the Year 2000 date problem and computerized medical devices. He defined the types of medical devices that are subject to Year 2000 problems and explained the definition of Year 2000 compliance. He asked the panel to provide advice regarding problematic devices, identify types of devices that could present risks to patients because of date problems, and suggest actions to reduce risks from Year 2000 problems.

Dr. Brown summarized FDA/CDRH activities on the Year 2000 problem to date. He noted that the FDA has a biomedical equipment database on its World Wide Web site that is continually updated and contains voluntary submission of data provided by manufacturers. The database shows that many companies have not yet reported. Most of the noncompliant products have date stamping problems, which is a less serious issue, but a limited number have operational problems. Manufacturers are providing a variety of solutions. The FDA can recall devices presenting a significant risk to public health and will monitor reports of Y2K problems with emphasis on devices that could present significant patient risks. Dr. Brown listed future CDRH/FDA activities and healthcare facility issues and asked the panel to give the problem serious consideration.

OPEN PUBLIC HEARING

There were no requests from the audience to address the panel.

SPONSOR PRESENTATION

Jim Connolly, president of Polymer Technology Systems, Inc, gave a brief history of the company and its efforts to develop a device with a multi-test menu that produces hospital-quality results for diabetes management. He described the device and its principles of operation, noting that the device is a single instrument measuring a small blood sample with multi-test papers. Mr. Connolly summarized statistics on diabetes and the relationship of triglycerides and other lipids to it and to cardiovascular risks. He presented results from the Paris Prospective study, which linked triglycerides rather than cholesterol to the risk of heart disease.

Dr. Mark Deeg discussed the clinical significance of measuring triglycerides and the role of triglycerides in heart disease, whether as an independent or synergistic risk

factor or metabolic marker for it. He presented results from the Copenhagen Male Study, the Framingham Heart Study, and the Helsinki Heart Study, as well as clinical trials at the VA and concluded that there is increasing evidence that triglycerides are an independent risk factor in heart disease and an important one for women and diabetics. Whether it is a synergistic factor or a metabolic marker, clinical trials show a benefit from lowering triglycerides. He recommended that measuring triglyceride levels should be part of a global risk assessment done by physicians and a target to help guide therapy for coronary artery disease, as well as a clue to other diseases. For patients, triglyceride measurement provides a target and a means to assess lifestyle changes and improve compliance with treatment regimens.

Sunil Anaokar presented information on test procedure and use and on performance data. **Dr. Jim Pasqua** discussed total system error, noting that they did not meet the NCEP guidelines and negative bias that could be resolved as needed. **Margo Enright** discussed aspects of the labeling such as presentation of total system error, intended use and accuracy statements, and user guides and package inserts. **Mr. Connolly** concluded the sponsor presentation by summarizing the device performance as providing few risks and good benefits for the patient.

Question and Answer Period

Panel questions focused on device variability in the hands of consumers, accuracy, labeling questions, and where the device fits into the pattern of patient management. The panel expressed concerns over testing materials, limitations, interference from other drugs or vitamins, and lack of comparison to a reference method.

FDA PRESENTATION

Arleen Pinkos, FDA reviewer from the Clinical Chemistry and Clinical Toxicology Branch, gave an overview of the special considerations given to OTC devices and summarized some of the performance studies. Ms. Pinkos discussed the determination of substantial equivalence between a predicate and a trial device. She noted that OTC product evaluation includes assessment of performance characteristics, consumer use factors, interpretable test results, and the benefit-to-risk ratio. In summarizing the key performance studies done, Ms. Pinkos presented performance goals identified for triglycerides by the National Cholesterol Education Program (NCEP), noting that the NCEP recommends that the accuracy of triglyceride assays be characterized by the reference method of the Center for Disease Control (CDC). She presented results of the sponsor's accuracy studies, precision studies, and interference studies.

Carol Benson of the FDA discussed total error calculations, presenting three scenarios for estimating total error and giving estimates based on those scenarios. The total analytical error estimates using the total coefficient of variation from the precision study using control materials performed by professionals ranged from 22.1% to 28.8%. The total error estimates using the lowest and highest within run coefficient of variation from the precision study using whole blood performed by consumers ranged from 14.8% to 24.6% and 26.8% to 30.5%, respectively.

Dr. Telba Irony of the FDA did a statistical analysis of the precision studies done by three consumers on two levels of whole blood each, noting a huge variation in results. She analyzed confidence intervals, noting uncertainty about the estimated

standard deviations, and random error based on a small sample over a short time period.

Dr. Irony concluded with a comparison of methods between the BioScanner device versus the CRMLN lab reference based on 220 patients.

Dr. Henry Ginsberg, guest speaker, discussed lipids and the role of triglycerides in assessment of cholesterol and its effects on coronary disease. He noted that the total cholesterol level does not change much from day to day, but the triglyceride level does. There is also postprandial variability in triglyceride level, which is useful to know. He discussed results from the Copenhagen, German, and VA studies. In general, Dr. Ginsberg stated, it is useful to increase self-knowledge and self-empowerment about triglyceride or cholesterol levels and that self-screening, especially based on nonfasting results, could result in more at-risk consumers seeking medical advice.

Questions and Answers

In answer to panel questions, Dr. Ginsberg suggested that the best use for the device would not be for weekly or even monthly home testing or for type 1 diabetics. He suggested that the device might have some utility if a person would not see their doctor for four months or so. He also noted that he did not see the reasoning behind use with postmenopausal women since most postmenopausal women do not have dyslipidemia.

Ten questions for panel discussion were read to the panel for their consideration. One panel member stated that the central issue was whether the compromise in performance was outweighed by OTC access or not. Other panel concerns included interference from ascorbic acid, elevated hematocrits, or other drugs.

OPEN PUBLIC HEARING

There were no requests from the audience to address the panel.

OPEN COMMITTEE DISCUSSION

The panel agreed that the Agency's requirement for comparison to a CDC reference laboratory is reasonable when the device is for OTC use, both for comparison and traceability. The majority of the panel also agreed that an OTC device should be required to meet NCEP performance goals or some modest modification of those goals, although one member disagreed, saying that it was sufficient if labeling accurately and comprehensibly portrayed device performance. The panel also agreed that the appropriate minimum sample size depends on bias calculations and that there should be minimum requirements for sample distribution. The panel suggested using the NCCLS guidelines or approach to help set minimum sample distribution and including more values based on clinical decisions/cut points. The analysis should be sufficiently powered within each range. It was also suggested that more samples be added in the 400-500 mg/dL range.

The panel thought that the sponsor had not done the appropriate precision and interference studies. The precision studies need more numbers, and the interference studies should focus on specific effects of drugs diabetics take, certain classes of drugs, metabolites, pore size, and ascorbic acid. One panel member felt it was unfair to weigh heavily on precision if it is performed by untrained users. The panel also suggested a need for more standard NCCLS type spiking experiments.

The panel thought the appropriate claim for the device was not captured in the labeling as it stood and stated that the labeling should reflect the panel discussion. The panel suggested that the labeling include a recommendation that patients consult their physicians after the test. Labeling statements about precision and accuracy statements should incorporate the statistician's comments; one suggestion was that labeling should

include references to accuracy plus or minus that of the reference method. The size of the samples used should be a statistical consideration. The intended audience for the device should be restated, and age limits for the population using the device should be specified. Use of the device should be consistent with ADA and NCEP guidelines.

The panel unanimously agreed that device performance is not adequate to support the intended use because of the number of false positives and negatives. Members also agreed that the current labeling does not convey performance of the device properly. The panel also unanimously recommended that the quality control instructions be clarified and the lay and professional inserts be combined and written more clearly. Dr. Rosenbloom made a number of specific suggestions about rewording references to triglycerides as fats, to discarding the strip, and to in vitro testing, as well as the need to eliminate jargon and typographical errors. The members also agreed that the device's risks outweigh the benefits in its current form, although that ratio could change if reliability, accuracy, and precision could be improved.

A statement from Dr. Kroll was read that said the device failed to adequately characterize performance and to meet NHLBI lipid standardization program criteria. The imprecision was too high, there needs to be an evaluation of other interferents, and the appropriate sample population was not used.

Final Questions

There were no final questions.

Sponsor Remarks

The sponsor representatives stated that they intend to revise the device based on panel recommendations. They will address the statistical issues raised, including

calibrating against the CRMLN method and using more high-end samples to meet the NCEP guidelines more closely. They intend to address the labeling recommendations such as intended users, frequency of testing, and referral of device users to physicians, as well as looking at drug inference results and combining the professional and OTC package inserts.

FINAL RECOMMENDATIONS

Dr. Nipper noted that these had been made through the questions discussed. There were no additions.

Dr. Gutman thanked the panel and said the FDA would work with the sponsor to include panel suggestions in the device revisions.

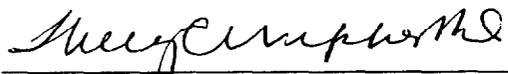
Veronica Calvin thanked the sponsor, FDA staff, and the panel and announced that the next meeting will be December 6-7, 1999. Dr. Nipper also thanked the panel, staff, and sponsors and adjourned the meeting at 4:35 p.m.

I certify that I attended the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel on October 28, 1999, and that these minutes accurately reflect what transpired.



Veronica J. Calvin
Executive Secretary

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



Henry C. Nipper, Ph.D.
Chairperson