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SUMMARY MINUTES

MEETING OF THE CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

OPEN SESSION

OCTOBER 29, 2001

Meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel

Attendees

October 29, 2001

Chairperson
Martin H. Kroll, M.D.

Executive Secretary
Veronica J. Calvin, M.A.

Members
Stephen Clement, M.D.
Cassandra E. Henderson, M.D.
Barbara R. Manno, Ph.D.
Arlan L. Rosenbloom, M.D.

Consultants
Andrew J. Ahmann, M.D.
Jose F. Cara, M.D.

Consumer Representative
Davida F. Kruger, R.N.

Industry Representative
Fred D. Lasky, Ph.D.

Patient Representative
Diane Lellock

FDA Representative
Steven I. Gutman, M.D., M.B.A.

Guest
Bernard E. Statland, M.D., Ph.D.
Director, Office of Device Evaluation

CALL TO ORDER

Chairperson Martin Kroll called the meeting to order at 8:05 a.m. and introduced Bernard E. Statland, M.D., Ph.D., director, Office of Device Evaluation, FDA. Dr. Statland thanked the people responsible for pulling the meeting together and noted that although alternative site testing (AST) of blood glucose has produced some excellent benefits for patients, it may not be as accurate as it needs to be.

Executive Secretary Veronica Calvin read the conflict-of-interest statement. Panel member Davida Kruger had financial interests in firms at issue that were related to the day's agenda but had received a conflict-of-interest waiver and could participate fully in the meeting. Panel members Martin Kroll and Arlan Rosenbloom had past or current interests in firms at issue for matters that were not related to the day's agenda and therefore could participate fully in the meeting. The agency had also determined that Jose Cara had past interests in firms at issue for matters that were related to the day's agenda, but because the meeting's agenda involved general matters, he could participate fully in the meeting. Diane Lellock, patient representative, had acknowledged personal financial interests in a firm at issue. Ms. Calvin then reviewed the outcome of the panel's November 13-14, 2000, meeting.

FDA PRESENTATION

Patricia Bernhardt, B.S., MT(ASCP), scientific reviewer, Division of Clinical Laboratory Devices, Office of Device Evaluation, described the FDA's concerns with AST glucose measurements. She explained that the research on the devices that use blood samples drawn from sites other than the fingertip (i.e., the forearm, upper arm, thigh, calf, or base of the thumb) demonstrates discordance (i.e., lack of agreement) with fingertip measurements. In some cases,

the differences are so marked that fingertip samples may produce readings in the hypo- or hyperglycemic range while the AST sample results are in the normal range.

Ms. Bernhardt said that the FDA wants to be sure that patients with diabetes will be able to use the devices in an appropriate manner and that the devices provide users with the information they need to manage their diabetes. The FDA's current review process evaluates testing under conditions of hypo- and hyperglycemia, but it does not evaluate testing during rapid glucose changes. Also, the FDA does not know whether harm has occurred as a result of AST because Medical Device Reporting (MDR) data do not differentiate between sampling sites. The FDA became aware of the problem of discordance when manufacturers who market or plan to market the devices submitted information on the issue and possible solutions to address it.

Ms. Bernhardt then presented information on several different data presentation formats: Clarke Error Grid Analysis (EGA), time-elapsed plots, Bland-Altman plots, and linear regression graphs.

Ms. Bernhardt explained that FDA reviewers had identified several points that they thought should be addressed when developing guidance to standardize the review of 510(k) applications involving AST devices:

- Blood glucose testing before meals, regardless of the device used, demonstrates comparable results for fingertip samples and AST.
- When discordance occurs, it is observed after meals. Some patients, regardless of the device used, demonstrate comparable blood glucose levels between sampling sites some of the time, even when blood glucose is not in a steady state.
- Testing has not been performed at night, and the effects of exercise and concurrent illness have been tested only in a limited way.

The FDA needs the panel's input in determining whether an appropriate study design should address those issues. Bernhardt then presented the questions before the panel.

FDA PRESENTATION

Marina Kondratovich, Ph.D., mathematical statistician, Division of Biostatistics, Office of Surveillance and Biometrics, presented a statistical overview of the various types of data presentations FDA has seen in the 510(k) submissions for AST devices. She described the different study designs in the applications and discussed the various statistical analysis techniques. She said that the panel should consider four aspects of study design in its deliberations: type of measurement (i.e., single-point measurements vs. time series), state of glucose level (i.e., steady, stabilizing, or dynamic), rate of glucose change, and patient characteristics.

SPONSORS PRESENTATIONS

Nina Peled, Ph.D., M.B.A., vice president, scientific affairs, Amira Medical, described research on the performance and comfort of the AtLast blood glucose testing system in testing blood samples taken from the palm of the hand. Compared with fingertip testing, the palm provided both lag-free glucose readings and pain-free testing. Amira's series of studies involved participants in a steady glycemic state, participants in random glycemic states, participants going through rapid changes in glucose levels, and participants going into hypoglycemic states. In all four studies, palm samples provided results that compared favorably with fingertip samples. Dr. Peled presented data as linear regression analyses and time course data, all of which demonstrated a close fit of the palm data to fingertip testing data. In addition, EGA indicated that

testing with blood samples from the palm could provide timely detection of hypoglycemia. An additional study asked patients to rate the comfort of the AtLast device; 76% of the participants preferred the palm over the forearm as a test site, and 67% reported no pain with the device. Dr. Peled concluded by asking that the FDA immediately clear the AtLast device without labeling restrictions.

Ron Ng, Ph.D., DABCC, FACB, director, medical and clinical affairs, Abbot Laboratories, MediSense Products, presented data on the accuracy of the Sof-Tact system for testing blood glucose in samples taken from the forearm. The Sof-Tact device increases perfusion by creating a vacuum over the sampling site. EGA of a clinical study of lay users demonstrated that the accuracy of the Sof-Tact system was clinically acceptable. Dr. Ng also described results of a meal tolerance test, an oral glucose tolerance test, and a hypoglycemia study designed to evaluate the accuracy of the device; in all three studies, EGA indicated that between 99.5% and 100% of the Sof-Tact results were clinically acceptable. Dr. Ng concluded by saying that the data support use of the device in both static and dynamic glucose conditions. Each manufacturer should characterize its device in both static and dynamic conditions with labeling appropriate to performance.

David L. Horwitz, M.D., Ph.D., vice president, medical and regulatory affairs, LifeScan, Inc., described studies on the One Touch Ultra System. He presented time series data comparing blood glucose levels obtained from fingertip samples (analyzed according to the Yellow Springs Instrument [YSI] method) with results from samples obtained from the fingertip, forearm, and thigh analyzed using the One Touch Ultra system. The study found that AST before meals gave accurate results in nearly all patients; postprandial testing, however, did not always give concordant results. A second study of a group of patients who had participated in the first study

produced results that were consistent with the first study but which confirmed day-to-day intrasubject variability in discordance. Dr. Horwitz noted that the study results indicated that the greater the rate of change in glucose levels, regardless of direction, the greater the difference between AST and fingertip sample readings. As with other studies, most of the participants tested in the LifeScan studies (79%) expressed a preference for AST. Dr. Horwitz also described a LifeScan study conducted in Europe that involved patient at-home comparison of finger and arm testing; most patients (80%) had less pain or no pain with arm testing compared with fingertip testing. EGA of the data from the European study showed that 96% of all data points were in the A or B zone, regardless of when the samples were drawn, and that 99% of the points were in the A or B zone when fasting samples were analyzed. Finally, Dr. Horwitz presented LifeScan's recommendations: (1) Data in any studies recommended by the panel should address normal perturbations in glucose and specific anatomic sites; and (2) labeling should include information on expected variations, appropriate timing of AST, and cautions about hypoglycemia. Dr. Horwitz presented two labeling options for the panel's consideration along with data indicating that patients understand the proposed labeling.

Sara Weaver, R.D., marketing manager, LifeScan, Inc., described the company's patient and physician education programs. The company educates consumers and physicians through conference presentations, brochures, and direct mail, among other techniques.

Dr. Kroll asked the panel members whether they had any questions for the presenters. Dr. Cara asked Dr. Peled whether any children under age 14 or 18 had participated in the Amira studies. Dr. Peled responded that arm sampling had been used in very young children with acceptable accuracy 2 hours postprandial. Dr. Horowitz said that the LifeScan device had been

tested on children as young as 8 years old and that equivalent results had been obtained for arm and finger testing.

Dr. Manno asked whether any of the Amira studies had noted differences between patients who had highly calloused palms and those who did not. Dr. Peled responded that the Amira research took place in a farm community and that many of the participants had calloused palms; however, no differences were found related to calloused palms. Dr. Manno also asked how old the oldest patients were in the studies. Dr. Peled responded that the patients in the Amira studies were up to 64 years old, and Dr. Ng indicated that some of the patients in the MediSense studies were age 70 and older.

Dr. Henderson asked whether any issues related to capillary fragility had arisen in the MediSense study, and Dr. Ng said no. He noted that of the two MDR reports received on the device, one involved bruising; in the study, however, no problems were seen. Dr. Henderson asked how many Sof-Tact devices were in use, and Dr. Ng responded that thousands had been distributed in the United States and abroad. Finally, she asked whether any studies had been conducted on pregnant patients, and Dr. Ng said that although that group was not studied specifically, it was conceivable that some of the participants were pregnant during the research.

Dr. Rosenbloom asked whether the duration of diabetes was a factor in the studies, given that thickening of the skin can occur with long-term diabetes. (He also noted that technically, the correct term is *alternative* site testing, not alternate site testing, as many people use.) Dr. Horowitz said that the LifeScan found no connection between the accuracy of the One Touch Ultra system and duration of diabetes. Dr. Rosenbloom then asked whether the Sof-Tact device might have different functional characteristics for people with stiff forearm skin, but Dr. Ng responded that so far, no difference in functionality had been seen.

Dr. Ahmann asked whether the relative means were available for the pain comparisons of palm testing and arm testing, but Dr. Peled indicated that she did not have those data. Dr. Ahmann also asked whether Amira's research had addressed the concomitant use of medications such as aspirin and beta blockers, and Dr. Peled responded that it had not.

Ms. Lellock asked for clarification of the meaning of "vigorous rubbing," which Eve Conner, Ph.D. (a speaker scheduled for after the morning break) provided. Dr. Ng pointed out that the Sof-Tact device had been designed so as not to require rubbing.

Dr. Cara wanted to know whether LifeScan had attempted to evaluate what percentage of patients actually read the labeling, and Dr. Horwitz replied that it had not. Dr. Clement noted that LifeScan had given considerable thought to labeling and asked whether Dr. Horwitz would recommend using fingertip testing instead of AST if hypoglycemia was suspected, before meals, and after exercise. Dr. Horwitz replied that most patients can tell if their glucose level is changing rapidly and that issues related to hypoglycemia are addressed in LifeScan's labeling recommendations. Dr. Rosenbloom, however, noted that labeling is confounded by intrapatient variability: Even experienced patients cannot always tell when they are undergoing rapid blood glucose changes.

Eve Conner, Ph.D., vice president, quality assurance/regulatory affairs, TheraSense, Inc., presented data on her company's FreeStyle system. The data demonstrate the safety and effectiveness of AST; AST meets important patient needs; an adverse event rate of only one per 3 million tests has been reported; and the product is properly labeled. The benefits of AST outweigh the risks.

Geoff McGarraugh, director of chemistry, TheraSense, Inc., presented data on clinical studies of the FreeStyle system as used with blood samples from the forearm. Time course

studies indicated that the glucose levels for the arm samples lagged those of the fingertip samples by approximately 20 minutes, but the lag was made clinically insignificant by rubbing. Because the lag is not always eliminated by rubbing, however, the "simple, conservative" instructions are to use fingertip samples if hypoglycemia is suspected. Six-month outcome studies demonstrated that glucose control was maintained with the FreeStyle system. Moreover, three-fourths of the participants preferred arm testing. Mr. McGarraugh disputed the findings of two studies not sponsored by TheraSense that contradicted his company's findings; he said that the design of both studies was flawed, and he presented data to support his assertions.

Dr. Conner described TheraSense's approach to labeling and presented a slide of an attention-getting label included in the FreeStyle packaging intended to motivate the user to read the labeling. She noted that the current labeling informs the user about the potential physiologic lag, explains when lag might be expected, provides the user with simple instructions for minimizing the lag, and recommends fingertip testing when testing for hypoglycemia or if the user has hypoglycemic unawareness. Labeling comprehension studies, outcome studies, and user experience all indicate that patients understand the labeling well. The rate of serious adverse events is very low, and no adverse event sequelae or deaths have been reported.

Martin Abrahamson, M.D., chief, Adult Diabetes, Joslin Diabetes Center, discussed his clinical experience with the FreeStyle device. AST is considerably less painful than and has comparable accuracy to fingertip testing, provides alternatives for people unwilling to test on fingers, and assists parents when testing children. AST increases compliance and thus helps patients manage their diabetes, and it has a clinically acceptable error rate.

Finally, Dr. Conner presented TheraSense's recommendations to the panel. The FDA should follow the current guidance document with regard to the data and data analysis required

for AST devices. Time series data could help determine relevant physiological issues. Labeling, too, could follow the general requirements in the current guidance document and should advise patients that AST differs from fingertip testing. Different devices should have different cautionary statements, depending on the data. Finally, 510(k) applications should include performance data to support claims; the devices should continue as over-the-counter (OTC) devices; manufacturers should be responsible for education of end users and health care professionals; and a public health notification is not warranted.

Luann Ochs, M.S., director, regulatory submissions, near patient testing, Roche Diagnostics Corp., described a series of Roche studies that found that AST measurements are equivalent to fingertip results if the patient's blood glucose is in a steady state. The studies also found that the differences between forearm testing and fingertip testing appear to be caused by physiological differences in the testing sites, which vary among patients. Roche's position is that AST is generally safe and effective for people with diabetes, but health care providers and device users need to understand how to use AST properly. With Roche's Accu-Chek system, 15% of hypoglycemic events were missed with AST, meaning that 5 of every 1,000 AST tests could be an undetected hypoglycemic event.

Ms. Ochs presented data from Roche's labeling comprehension studies for labels describing how to use Accu-Chek for AST; the studies found that patients had excellent understanding of the labeling materials. She stated that manufacturers can ensure that consumers receive the information on AST that consumers need. Finally, Ms. Ochs said that Roche recommends two paths for future 510(k) review. First, if a manufacturer agrees to precautionary statements, the review criteria should be the same as for a fingertip test; if a manufacturer

believes the precautions are not necessary for its device, however, it should provide evidence to that effect.

OPEN PUBLIC HEARING

Theodore Koschinsky, M.D., German Diabetes Research Institute, Dusseldorf, Germany, presented data from his study of AST. He tested the FreeStyle, Sof-Tact, and One Touch Ultra systems under conditions of extremely rapid blood glucose change. He found significant lag with each system, even when the site was rubbed. Results comparing base-of-thumb samples with fingertip samples showed minimal lag, however. Dr. Koschinsky stated that blood glucose kinetics in the thumb are identical to those in the finger. The observed differences in the results are not device specific and have to do with the testing site. Dr. Koschinsky provided information on the anatomy and physiology of capillary blood sampling to explain some of the differences in the results. Further AST research should include studies of the effects of rapid blood glucose changes in standardized experimental design for each device and for each alternative site recommended; incidence of AST failure in observational studies; characterization of patient-specific risk factors; and effects of various types of exercise in both experimental studies and observational studies. Dr. Koschinsky concluded by saying that any glucose-monitoring technology that depends on blood or interstitial fluid kinetics within the upper dermal compartment, such as optical and transdermal approaches, must be examined for the effects of rapid blood glucose changes.

Russell O. Potts, Ph.D., vice president of research and development, Cygnus, Inc., described the GlucoWatch, a glucose-monitoring device for adults with diabetes. He described the device's intended use, the reverse iontophoresis process that operates the device, and reasons for the differences between values ascertained by the GlucoWatch and other testing systems. He

concluded by saying that the GlucoWatch is a unique device that provides better detection of hypo- and hyperglycemia than do existing blood glucose meters.

Clare Rosenfeld, former national youth advocate for the American Diabetes Association, spoke about her experience with the One Touch Ultra system. She stated that it has helped her manage her diabetes and has improved her quality of life. When she first started using AST, she tested on both her finger and her arm. Because of her personal testing results, she feels confident in using either fingertip or arm samples when she feels that her levels are normal. When she is unsure, she uses fingertip samples. Ms. Rosenfeld said that the current labeling of AST systems offers the information consumers need to use the products safely.

Craig C. Orlowski, M.D., Department of Pediatric Endocrinology, University of Rochester, New York, stated that among his patients, he has found no instances of severe hypo- or hyperglycemia as a result of using AST. He believes that his patients are testing more often with AST because they have less pain than with fingertip testing.

Laura Billetdeaux of Children With Diabetes (CWD) and her son, Sam, said that AST has made a huge difference in how her son manages diabetes. She described how AST makes life easier both for parents of diabetic children and for their children. Ms. Billetdeaux summarized the results of two online CWD surveys, in which most respondents replied that AST was very or somewhat important in their diabetes management. Finally, she read several excerpts from letters from parents in support of AST.

Paul Madden, M.Ed., special assistant to the president, Joslin Diabetes Center, said that AST helps people manage their diabetes in part because it allows people to vary parts of their diabetes management program, thereby removing some of the boredom and giving them a feeling of greater control. AST also reduces pain, thus encouraging more frequent testing. Any

therapy that allows patients to check blood glucose more often will help them stay in the normal range, enhancing quality of life and improving health.

Dr. Kroll noted that the panel had received more than 30 e-mails from parents in support of AST.

OPEN COMMITTEE DISCUSSION

Dr. Kroll asked whether any of the panel members had questions for the TheraSense or Roche representatives. Dr. Henderson asked whether any studies had looked at patients with peripheral vascular disease or at pregnant women. Dr. Conner said that the TheraSense studies had a broad range of participants, from 5-year-olds to people in their 80s, and that the results for those participants were good. Two TheraSense studies are currently examining time series data in pregnant women with diabetes.

Ms. Kruger noted that if circulatory problems were an issue, one would see that in fingertip testing as well as arm testing. Dr. Rosenbloom asked whether skin bruising or skin fragility issues occurred with the Sof-Tact device. Paul Locke from the University of Massachusetts Medical School, one of the clinical researchers for several of the studies on the Sof-Tact device, said that more than one-third of the patients in his study were older than age 50. He did not see any problems with ecchymosis or bruising in elderly populations.

Dr. Cara said that he was pleased with the results of TheraSense's outcome study but was surprised to find that the willingness to test was no different for people using AST and people using fingertip testing. Dr. Conner replied that the participants were already in fairly good control of their diabetes, so it is not surprising that compliance did not increase significantly. Many of the participants preferred the FreeStyle device. Dr. Cara asked whether TheraSense had

looked at the correlation between symptomatic hypoglycemia and hyperglycemia as established by fingertip testing and AST; Dr. Conner said that TheraSense had not looked at that correlation.

Dr. Ahmann asked whether TheraSense had compared preferences of meters, and Dr. Conner said the company had not.

Dr. Clement noted that the therapeutic paradox of diabetes is that intensive insulin therapy saves lives but the risk of hypoglycemia increases as one gets closer to the target range. Self-monitored blood glucose data are critical for intensive diabetes treatment, and patients must be taught to use their own data. AST can provide useful information about glycemic control and can be a guide for titrating nighttime diabetes medication. Accuracy is important, and the burden of proof is on the companies. The technology has wonderful potential, and dynamic testing can help ferret out the differences.

Dr. Kroll reread the questions before the panel. The panel addressed each question in turn in a round-robin process.

1. **Should FDA's review of these devices include dynamic as well as steady-state data or are there more appropriate and less burdensome ways to address this public health issue? If additional data are necessary to characterize device performance:**
   - **What are appropriate study designs that will capture potential discordance during episodes of rapidly rising and falling glucose levels?**
   - **What is the minimum data set to be studied?**
   - **What are appropriate analytical or statistical tools to be applied to the data (i.e., standard regression analysis, Clarke Error Grid analysis, time elapsed plots)?**

Panel members concurred that dynamic studies are needed and that it is appropriate for FDA to review dynamic data before clearing the device for market. Many expressed the need for studies involving children, people with co-occurring health conditions or concomitant mediation use, the role of exercise. In addition, studies are needed to ascertain individual characteristics that could lead to discordance. Panel members suggested the need for additional time series data and studies using insulin challenges. Several members found it reassuring that no incidents of missed hypoglycemia have been reported.

Dr. Henderson stated that the devices are excellent clinical tools, but they need improvement. Ms. Kruger noted that the data indicate that companies are responsive to concerns and that it is important to remember that the devices represent an advance in diabetes care.

Dr. Clement noted that the discordance can be troublingly high. The methodology of glucose challenge followed by insulin is useful. It would be good to separate the data into upflow and downflow phases and to analyze the phases separately using Bland-Altman plots. If a company developed a method to minimize lag, it could say that the devices are substantially equivalent to fingertip testing. The devices have to be challenged in a rigorous way; random testing is not quite rigorous enough.

Dr. Kroll noted that diabetes is a dynamic disease—it cannot be evaluated in a steady state. It is important for studies to look at time course data as well as hypo- and hyperglycemia and insulin challenges and to get away from stationary statistics. In addition, not all people experience time lags; it is important to identify how significant the time lags are and how often they occur and to analyze them by group. People who do not experience lags do not need additional blood glucose testing.

Dr. Cara noted that people with diabetes hate few things more than blood glucose monitoring; AST is an important technology that needs to be explored. He cautioned the FDA against moving backward. Manufacturers could also look at other processes to increase perfusion besides rubbing, such as warming.

Dr. Lasky thanked the manufacturers for the comprehensive data they provided and said that it is important to analyze the data carefully; although it is helpful to look at average data, averages often mask data of concern. Agreement tables are helpful, but they are more static than dynamic. In addition, not every alternative site provides the same kind of information.

Dr. Cara said that manufacturers should address the dynamic nature of blood glucose monitoring. The outcome of monitoring is not an isolated number—it occurs in context. A better understanding is needed of some of the other factors involved in using blood glucose numbers for the most effective monitoring. EGA does not address those factors.

Ms. Kruger noted that one can ask only so much of manufacturers. It is the clinician's responsibility to know the different characteristics of his or her patients. In practice, diabetes is not what the book says.

Dr. Ahmann said that although much of the variation in the data comes down to interindividual variation, intradindividual variation is also an issue. Dr. Cara added that whatever device is being evaluated needs to be evaluated in a real-life situation.

Dr. Gutman asked the panel to identify the minimum parameters of a dynamic study. Dr. Clement described a protocol for an outpatient setting that involved giving the patient a glucose challenge and measuring the up slope; then administering insulin and measuring the down slope; and, finally, measuring the resulting error. In base-of-thumb samples, for example, the acceptable error rate could be ± 20%, 95% of the time. Dr. Clement remarked that fingertip testing remains the gold standard.

Dr. Kroll said that an additional type of study would be one in which manufacturers characterized individual lag. He suggested that stable lag in a person could enable the use of a higher value for AST to indicate hypoglycemia.

Dr. Rosenbloom said that it would be interesting to see a criterion based on discrepancies—the number of episodes hypoglycemia is identified (or missed) with fingertip testing versus AST; ideally, there should be no difference. More frequent testing should catch a greater number of hypoglycemic episodes.

Ms. Lellock said that if a person feels hypoglycemic, he or she should treat the hypoglycemia even if the results of a blood glucose test indicate otherwise—no test is perfect.

Dr. Cara added that having 3- to 6-month real-life experience with a meter is important; he would be pleased to see TheraSense's outcome data.

Dr. Lasky added that manufacturers have expressed universal agreement to work with the FDA to use each manufacturer's information. They see a real benefit to developing general guidelines and determining what clinical data would be needed to obtain FDA clearance of AST and related technology.

2. Should FDA require manufacturers to include strong cautionary labeling about this problem unless they provide data demonstrating that the discordance is unlikely to occur with their particular device?

Panel members agreed that the FDA should require manufacturers to include strong cautionary labeling.

Ms. Lellock liked TheraSense's red warning label. If manufacturers know that their devices lag behind fingertip testing, they should warn the consumer. If there is no lag, however, there is no need for a warning label.

Dr. Lasky agreed that manufacturers should provide cautions in labels, particularly for forearm samples, and added that he would like to see a better definition of "unlikely" because it has important implications for labeling. He noted that standard definitions for terms such as "possibility of occurrence" are used in the field of risk management and that many manufacturers rely on such definitions in their product development.

Dr. Cara noted that the meters have not been thoroughly evaluated for AST in women and children. He said that labeling needs to include information on fingertip testing, on hypoglycemia, and on what is still not known about using AST. Dr. Ahmann noted that the

information on thumb testing indicates that differences are a function of the collection site, not the meter itself.

Dr. Kroll agreed that a better definition of "unlikely" was needed. If it could be shown that AST was identical to fingertip testing, cautionary labeling would not be required. Labeling should emphasize that patients need to work with their physicians to establish whether they experience a lag. Unlike other tests, the results are specific to each user and could change over time with changes in microcirculation and so forth.

Dr. Clement liked LifeScan's proposed labeling—he remarked that "black-box" warnings just scare people. He added that the issue of whether patients' glucose is stable or unstable is an illusion. At certain times, fingertip testing is simply appropriate.

Ms. Kruger said that the companies had done a remarkable job of gathering data without the FDA saying that they had to. She suggested using the term "health care team" rather than "physician" in labeling.

Dr. Henderson said that labeling should mention the issue of lag; she believes that people either don't read black boxes or don't use the product. She would add a blurb titled "fingertip testing opportunities," which would list the times when such testing is indicated. Labeling should be a jumping-off point for the patient education process.

Dr. Rosenbloom noted that lag was unlikely to occur with testing at the base of the thumb. Labeling should state that patients should use fingertip testing instead of AST for sick-day management.

3. **Should FDA:**
   - **rescind the clearance for labeling for alternative site testing if the 510(k)s do not address this new scientific issue?**
   - **make these products prescription home-use?**
   - **require additional data and labeling changes?**

Some panel members felt that rescinding clearance should be an option if manufacturers do not address the issue of discordance. Dr. Lasky said that rescinding clearance is a difficult issue because the companies appear to have been forthcoming with the data. He noted that no adverse events have been reported and that manufacturers have been responding effectively and responsibly. Ms. Kruger said that the FDA should not rescind existing clearances because the FDA has to move forward. Dr. Henderson said that the data requirements should be in place for new applications; she was not sure that the FDA should rescind existing clearances. With regard to risk management, she noted that "unlikely" is not a difficult concept.

Members generally agreed that the devices should not require a prescription because doing so would create a burden for consumers and would not guarantee better patient education. Ms. Lellock, however, said that the meters should be prescription home-use devices because doing so could help ensure that everyone who purchases a meter receives proper training in how to use it. Dr. Rosenbloom asked whether one reason for requiring a prescription for AST devices would be to ensure third-party payment. Dr. Clement noted that the issue is moot because all insurers require prescriptions for reimbursement anyway, even for OTC medications.

Panel members agreed that they had adequately addressed the labeling issue in the second question. Dr. Rosenbloom asked Dr. Gutman whether meters that have not been tested for particular sites will need further testing. Dr. Gutman answered that FDA would explore that issue; FDA does not look at off-label use, only at uses for which manufacturers make a claim. Rosenbloom noted that AST is becoming a popular alternative—people will assume that whatever meter they have is good for their purpose, so the labeling should note that it is only appropriate for certain use. Ms. Kruger said that cautionary labels are not needed for meters not approved for AST. Dr. Clement suggested giving the sponsor two options: (1) accepting labeling

as discussed or (2) providing data from dynamic testing that indicate no systematic bias in the upslope and downslope or differences between YSI results and the AST device. Dr. Kroll emphasized that labeling needs to be prominent and that even with good labeling, some patients need considerable help with learning to use glucose-monitoring devices—the concepts are difficult for some people.

4. Are there other activities or issues that FDA should consider with regard to this important public health issue, such as:
- **a public health alert**
- **targeted postmarket surveillance**
- **educational outreach activities to stakeholders and other government and nongovernment entities to promote additional research in this area?**

The panel generally concurred that the FDA should consider the activities listed in the question, although the members had mixed views on the need for a public health alert.

Ms. Lellock thought that a public health alert would be useful because not everyone is aware of the lag issues, but Dr. Lasky said that an alert was not warranted because it could create a panic situation; it would not be good for patients to stop monitoring themselves. Dr. Ahmann said that any public health alert would have to be done cautiously—media coverage of the alert would magnify its impact. Dr. Manno and Dr. Cara agreed that a public health alert was not warranted.

Dr. Henderson thought targeted postmarket surveillance was important, particularly with regard to pregnant women and concurrent illnesses. Dr. Rosenbloom added that such surveillance is important for children, too. Dr. Ahmann indicated that targeted postmarket surveillance might be a good option; he is skeptical of the effectiveness of MDRs and said that they are not that helpful except to spot trends. In addition, it is not likely that people will blame errors on the meter. More companies should look at the base of the thumb as a test site. Dr. Lasky suggested separating postmarket surveillance from postmarket clinical studies and agreed

that studies on specific populations are warranted. Lasky noted that from an industry perspective, surveillance connotes regulatory consequences and that surveillance requirements are already in place in the form of MDRs.

Dr. Kroll noted that glucose measurement is a dynamic, time-dependent process and that old statistical techniques fail in this area; additional outreach is needed to promote research. Dr. Cara encouraged FDA to work with other agencies and organizations to get the information out to a broad audience. Dr. Lasky said that education and outreach efforts were warranted and noted that manufacturers were expected to work with the diabetes associations to carry out such efforts.

OPEN PUBLIC HEARING

Dr. Kroll read into the record a letter from Sonia Cooper, president of the Children With Diabetes Foundation. Her letter noted the advantages of AST for diabetic children and their parents in terms of reduced pain and better monitoring. In addition, children often do not wash their fingers before testing, leading to distorted readings; AST can address that problem.

C. Kurt Alexander, M.D., CDE, FACP, FACE, a physician in Indiana who was an investigator in the Roche study (but was not representing Roche at the meeting), said that the study was designed to determine whether fingertip readings and AST readings differed and whether it could be predicted who might demonstrate discordance. The study found that discordance could not be predicted. Alexander described different patient education inserts and noted that even physicians may not be aware of the differences between AST and fingertip testing. He asked the FDA to not restrict patient access to the new technology because it enhances adherence and because patients seek new opportunities in testing. He said that patients, diabetes educators, physicians, and caregivers need to be informed of the differences among testing sites and that some patient occupations may be inappropriate for AST (e.g., pilots, heavy

machinery operators, high-rise construction workers). Alexander said that the trend is toward increased postprandial glucose testing, which makes education regarding differences even more important. When new information becomes available, companies should be allowed to distribute it immediately. In addition, before recommending AST for specific populations, it should be tested in those populations.

Maria C. Matas-Chamberlain, R.N., a nurse and certified diabetes educator (CDE) who has had diabetes for 20 years, spoke in favor of AST, saying that it has been very helpful to her and that because AST is pain free, she has seen it motivate people to test their glucose. She emphasized that CDEs must be kept informed about the technology.

Natalie Bellini, R.N., CDE, said that she has had diabetes for 32 years. She spoke in favor of AST and said that it makes a huge psychological difference for diabetics.

Carolyn D. Jones, J.D., M.P.H., Advanced Medical Technology Association (AdvaMed), said that the AdvaMed Blood Glucose Monitoring Working Group strongly supports the development and use of AST technology. Clinical research has demonstrated the accuracy of AST; evaluations should simulate real-life conditions rather than extreme conditions. Jones presented AdvaMed's "points-to-consider" for FDA's use in evaluating AST systems:

1. Manufacturers should use the same accuracy criteria they use to assess differences between glucose meter and laboratory results from fingertip blood samples; the reference sample should be obtained at the fingertip regardless of the AST site.
2. Studies to confirm the acceptability of an AST site should be done under the proposed conditions of use. Postprandial blood samples provide an adequate range of glucose change to evaluate non-steady-state system performance. Performance claims should be supported by a statistically sound study.

3. Data specific to each proposed alternative site should be obtained, and labeling claims should be limited to the specific sites that have been evaluated. AdvaMed believes it is appropriate to establish a set of precautionary statements to include in labeling.
4. AdvaMed supports the continued use of current systems on the market and FDA clearance of new systems as long as manufacturers inform users of the limits of AST.
5. Manufacturers are in the best position to give the proper education and training to consumers.
6. Prescription use is not warranted for AST products.

Finally, Jones presented suggested language for labeling.

OPEN COMMITTEE DISCUSSION

Dr. Henderson remarked that she saw no controversy with AST; it seems to be a good tool, albeit an imperfect one. Dr. Gutman remarked that one of the uses of a panel was to provide that kind of feedback to FDA; he noted that what may have seemed alarming 6 to 8 months ago may no longer be so in light of newer information. However, challenges still lie ahead.

Dr. Clement observed that the term "hypoglycemic unawareness" is not a common term and that perhaps other language should be used to describe the condition.

Dr. Lasky noted the increased effort toward standardization of in vitro diagnostic products, particularly internationally. FDA has been active in the standardization process; any criteria that are relevant to AST use should draw on the document outlining criteria for whole-blood glucose monitoring that was developed as part of a working group on standardization and which FDA has been critiquing.

Dr. Kondratovich asked the panel members what they thought an appropriate study design might be. Dr. Clement responded that serially measuring the blood glucose of individual

patients while provoking hyper- and hypoglycemia would provide good information. Dr. Kroll concurred with Dr. Clement that time series data are necessary and that single data points are inadequate. Dr. Rosenbloom suggested that single-point measurements could be useful for accuracy studies, but Dr. Kroll noted that paired single-point values are valid only if they come from the same sample; a problem with other studies is that they do not always use the same sample.

ADJOURNMENT

Dr. Kroll thanked the participants and adjourned the meeting at 3:56 p.m.

I certify that I attended this meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel on October 29, 2001, and that these minutes accurately reflect what transpired.

Veronica J. Calvin

Veronica J. Calvin, M.A.
Executive Secretary

I approve the minutes of the October 29, 2001, meeting as recorded in this summary.

Martin H. Kroll

Martin H. Kroll, M.D.
Chairperson