

FOOD AND DRUG ADMINISTRATION  
Clinical Chemistry and Clinical  
Toxicology Devices Panel

Premarket Notification Submission  
For an Over-The-Counter Device  
For Measuring Fructosamine  
and  
Issues Regarding Self-Monitoring  
Blood Glucose Systems  
(Day Two)

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## TABLE OF CONTENTS

|  | <u>Page</u> |
|--|-------------|
| Opening Remarks, Introduction of Panel   | 1           |
| FDA Presentation - Impact of Quality Systems<br>Regulations - Kimberly A. Trautman | 6           |
| FDA Presentation - Human Factors Issues -<br>Ron Kaye, M.A.                        | 19          |
| Open Public Session -  |             |
| Ken Ervin  | 29          |
| Biocontrol Technology - Mr. David Purdy  | 43          |
| Thomas Pitts   | 47          |
| Patrick Cooper   | 52          |
| Roseanne Savol   | 59          |
| Donald Parker  | 67          |
| Glenn Pittluck, Medicines Incorporated   | 81          |
| Ed Kimmelman, Boehringer Mannheim Corporation                                      | 85          |
| Paul Fox   | 94          |
| Dr. Frederick Kiechle, ASCP  | 136         |
| Jim Nichols, American Association for<br>Clinical Chemistry                        | 151         |
| Open Committee Discussion  | 163         |

P R O C E E D I N G S (8:10 a.m.)

**Agenda Item: Opening Remarks, Introduction of Panel**

MS. LAPPALAINEN: I am Sharon Lappalainen, executive secretary of the Clinical Chemistry and Clinical Toxicology Devices panel. We are here this morning to discuss the issues surrounding self-monitoring of blood glucose or SMBG systems, glucose meters and test strips. The goal of the meeting is to solicit information and suggestions from the panel, professional organizations, industry and consumers that will help identify how patients are currently being managed, determine what goals are appropriate for different groups of patients and different treatment regimens, determine what device performance is needed for support of these goals, discuss current technology and its performance capabilities and limitations and identify areas in which the agency, professional groups, patients and manufacturers can work together to help achieve the various goals of glucose monitoring and contribute to increased quality patient outcomes.

Topics of discussion will include:

1. Improvements which can be made in the pre-market review of these products, including changes warranted

in review criteria and their application.

2. Identification of realistic expectations for the physician and user of these devices based on current technology and determination of testing needed to assure product quality. Discussion will include consideration of both existing technical limitations and the potentials for changes in glucose measuring technology in the future.

3. Improvements which could be made in the pre-market product testing to provide a more realistic evaluation of actual performance in the field.

4. Possible improvements in the labelling of these devices to better reflect the expected performance in the home setting.

5. Steps that could be taken to improve the use of quality control measures in the home setting.

6. Other mechanisms available to FDA or other organizations to improve the practice of blood glucose monitoring in the home.

7. And lastly, improvements that could be made to FDA's existing guidance document entitled review criteria for assessment of portable blood glucose monitoring, in vitro diagnostic devices using glucose oxidase, dehydrogenates or hexokinase methodology, draft version 2-

14-97.

At this time I would like each of the panel members to introduce themselves. Please state your name, affiliation and your current FDA panel advisory membership. We will start with Dr. Habig.

DR. HABIG: Good morning. My name is Robert Habig. I am director of corporate regulatory affairs at Becton Dickinson and Company and I am the non-voting industry representative for this panel.

MS. ROSENTHAL: My name is Ellen Rosenthal. I am an engineer and I am a consumer rep. to this panel.

DR. FALLS: Good morning. I am Dr. Beverly Harrington Falls. I am an OB-GYN with Cornerstone Health Care in High Point, North Carolina. I am a voting member of the panel.

DR. CLEMENT: Good morning. I am Dr. Steve Clement, an adult endocrinologist here at Georgetown University and I am a voting temporary member of the panel.

DR. BOUGHMAN: Joann Boughman, vice president for academic affairs and dean of the graduate school, University of Maryland, regular voting member of the panel.

DR. REJ: I am Robert Rej, director of clinical chemistry and hematology and the New York state Department

of Health and associate professor at the School of Public Health, the State University of New York at Albany and I am a regular voting member of this panel.

DR. GOLDSMITH: Good morning. I am Barbara Goldsmith. I am the associate director of the Department of Laboratory Medicine at St. Christopher's Hospital for Children in Philadelphia and I am a voting member of this panel.

DR. COOPER: I am Jim Cooper. I am a geriatrician. I am senior medical advisor at the Agency for Health Care Policy and Research and I am also on the faculty of Uniformed Services University of Health Sciences and I am a temporary member.

DR. GUTMAN: I am Steven Gutman and I am the director of clinical laboratory devices.

DR. ZAWADZKI: Good morning. I am Joanna Zawadzki. I am an endocrinologist in private practice in Rockville, Maryland. I am also clinical associate professor of medicine at Georgetown University and I am a former member of the FDA endocrine and metabolic advisory committee.

DR. KURT: Good morning. I am Tom Kurt. I am a clinical professor of internal medicine at University of

Texas Southwestern Medical Center, a founder of the regional poison center that is at Parkland Hospital and a former FDA medical officer. I am a regular member of the panel.

DR. ROSENBLOOM: I am Arlen Rosenbloom. I am at the University of Florida at Gainesville, pediatric endocrinologist and I am a voting temporary member of the panel.

MS. LAPPALAINEN: Additionally, I would like to state that for the meetings today, Ms. Ellen Rosenthal will serve as consumer representative and Dr. Robert Habig will serve as the industry representative. The following are our current members on the panel: Dr. Joann Boughman, Dr. Barbara Goldsmith, Dr. Robert Rej, Dr. Thomas Kurt and Dr. Beverly Harrington Falls. I would like to state for the record that the following individuals are the temporary members on the panel for today: Dr. Joanna Zawadzki, Dr. Steven Clement, Dr. James Cooper and Dr. Arlen Rosenbloom.

That you, and now I would like to turn the meeting over to our distinguished chairman, Dr. Henry Nipper.

DR. NIPPER: Thank you. I am Henry Nipper. I am from Creighton University and I am honored to be chairperson of the meeting today.

We are continuing our consideration of cell

monitoring blood glucose systems today and we are going to have two 15-minute presentations from the FDA which I will introduce in just a moment and then after that we will have a morning of and an early afternoon of open public session in which some manufacturers self-monitoring blood glucose meters and devices will present their points of view.

I will do my best to be a bit by their time today. We started just a hair late and I apologize for that but we are also honored to have a camera crew from the Food and Drug Administration today who are playing with a little red wagon and a camera over there and they are making a training tape to make it easier for panel members to understand what kind of mess they are getting themselves into when they join an august group like this.

I am glad you are here today and I am sure that they are going to do, have a really good product for all of us to see except for the people they picked to film between 7:00 and 8:00 this morning which is why you couldn't get in here. You kept trying to get me to get it right.

Okay, are we ready for the FDA to talk? Kimberly Trautman is here. Good. Kimberly is a quality system expert from the Office of Compliance in the CDRH and we are happy to have her here to talk about the impact of quality systems

regulations. Ms. Trautman.

**Agenda Item: FDA Presentation - Impact of Quality  
Systems Regulations - Kimberly A. Trautman**

MS. TRAUTMAN: Thank you very much. Good morning. I have 15 minutes to talk to you and I am going to give you just a brief overview but I would really like to entertain any questions that you may have because I think that is really important for the panel.

So first I would like to tell you that GMPs are good manufacturing practice requirements have been in existence for medical device, finished device manufacturers since 1978. After 19 years, we have not revised that regulation for the first time and have revised it in what we call our quality systems regulation that goes into effect June 1, 1997. Our old regulation is still actually in effect today.

But the reason for, the major reason for the revision of the quality system regulation was the fact that Congress gave us authority in 1990 to add pre-production design controls to our review of finished device manufacturers and I think this may be important you when you are taking into some of your considerations of labelling and some specifications because design controls add a great

benefit, not only to the industry but to the FDA in looking at a product from birth to death.

Before, what we usually were looking at in our good manufacturing practices when an FDA inspector went into a finished device manufacturer was really what they were doing on the manufacturing floor to manufacture a finished device. Now, with the new regulation, we will also be looking at how and what kind of controls were used in the design of a device all the way from its birth, all the way through the progress, while the glucose monitors for home use wouldn't use servicing, but all the continuation of post-market surveillance and so forth to the death of that device and this may be very important for you when you start thinking about labelling considerations because when we talk about design controls, we are not talking about just the design of the product itself but the design of the product, its labelling, its packaging, its manufacturing processes, its QA tests all together.

And there is a lot of controls that can help eliminate problems up front if the manufacturer does this correctly and follows the regulation.

There is a couple of things that I noticed in the guidance that I would like to also tell you that are GMP

requirements our quality system regulation picks up on. Software verification and validation is mentioned in the guidance document. This is also a requirement for finished device manufacturers to have software validated whether that software used in the finished product or software used as part of the manufacturing of quality systems. We feel that software validation is the only way to assure reproducible results and so on only would our Office of Device Evaluation be looking at it, at software for certain particular specification reasons but when our field investigators go out, we will also be looking at that software validation to make sure that the manufacturer has used appropriate control mechanisms in developing that software.

A couple other things in the guidance document that I noticed that might be of interest. I am sure when we are talking about calibration tests and so forth that you are thinking of what calibration is being used to actually analyze some of the diagnostic aspects of the reagents but the quality system not only talks about the design of the product but it also has requirements that everything that the manufacturer is using to develop that product has to be calibrated. It talks about accuracy and precision limits and so it goes all the way from the start of the

manufacturing until it goes out the door so any products that are used for finished device testing would also have to be calibrated.

The whole concept of a quality system is to try to prevent during manufacturing problems up front before the product goes out the door. There are several aspects of the quality system. The lowest aspect is the test and inspection. There is lots of literature out there. Dr. Juran and quality experts teach the test and inspection during finished product development really is the least preferable manner because you really, even if you 100 percent test every product before it goes out the door as a manufacturer, you still are only likely to catch 80 percent of all the product defects so you need a little bit more and that little bit more is often described as the quality assurance system.

Quality assurance starts bringing in some of the aspects like I talked about using calibrated pieces of equipment, making sure that the engineers and the people on the manufacturing line are trained, having the appropriate environmental controls to make sure that different particulates in bioburden may not affect your finished product as it is going through manufacturing.

Complaint handling procedures. Procedures in place to take in information from the customers, determine if there is a problem, if there is a problem take the appropriate corrective actions.

Now, that is quality assurance and now what we have moved to in the new regulation like I said, is more of a total quality system which we refer to as a quality system which is the birth to death, from the design all the way from transferring that design to manufacturing, from making sure you have the appropriate purchase contracts with your component suppliers, making sure acceptance of those components or reagents are proper with the appropriate specificity, going all the way through to in process testing, finished device testing, distributing the product. Once the product is distributed, making sure that complaint handling systems are in place to handle any post-market surveillance information or feedback.

Having a corrective action system in place to make sure that if there is something that the complaints are showing that corrective action has been taken and this is a continuous feedback loop and we talk about now we have a system in the new regulation which is closing the loops. So everything kind of ties back on itself and hopefully that

will provide the best quality of a product as a finished device going out to the public.

So that is just a general overview and I know we don't have a whole lot of time for questions and answers so I would rather see if there is anything in particular on your minds that I may be able to help you with along the quality system regulation requirements.

DR. NIPPER: I think that Ms. Trautman has thrown the meeting open for questions. Is there any person on the panel who has any questions for her? Yes.

DR. KURT: My name is Tom Kurt. I am interested to know whether or not glucose monitoring devices are required to be registered so in post-marketing surveillance the problem is encountered that the current owners of such devices can be notified.

MS. TRAUTMAN: There is a registrational listing regulation separate and that would depend on the classification that a product would be set up but for most finished devices, a home use product would have to be registered with the FDA, a manufacturer would be registered and they would list the type of products. But what I think you are asking is you are more interested in the traceability of a particular product down to a particular

patient.

In the act, in the Food, Drug, Cosmetic Act, we are limited to how much we can mandate a manufacturer as far as tracing it down to the user needs. Only on some very high risk products where there is an unreasonable risk to the public health and that is a very high threshold for us, can we mandate traceability all the way to the end user and there is a tracking regulation which tracks several implantable devices to the end user.

However, the quality system regulation has a requirement for traceability and what that requirement under the quality system regulation does is it says a manufacturer has to be able to trace that particular product to the initial consignee, the initial consignee being the first person outside of his control. So that may be a distributor, it may be a particular hospital.

But what it is is it at least provides some control mechanism and there is some control numbers so when a hospital does get a home or a patient goes and purchases it off of a shelf, there is some control numbers that are on that package so that if there is a problem through that control number, the quality system regulation requires the manufacturers to have what we call a device history record.

That device history record basically says how that product was produced and how all the data and everything came out in that production and shows how it meets the original procedure of the manufacturer so that control number on that product that goes to the patient, they can trace back and look at the manufacturing record and say these were the incoming reagents used, these were the type of tests, this is how much or how little or how close it passed. Was it in the middle of my passing range? Was it stressing my passing range as far as specificity so there is some traceability aspects that are provided in quality system regulation.

DR. KURT: Do you know of any glucose manufacturers or monitoring manufacturers who independently include a card in the device that they are selling for marketing purposes, so they could market a future device or reagents to the end user of the product.

MS. TRAUTMAN: You are asking if they put a card in there and asking what? Asking for feedback?

DR. KURT: To send in your name and address for warranty purposes and then they would send out, for instance, marketing information.

MS. TRAUTMAN: That would be completely the manufacturer's option. There is nothing in the quality

system regulation that would require them to do that.

Whether I am familiar with that, the answer is no, but that doesn't mean that it doesn't exist.

DR. HABIG: Dr. Kurt, having worked for one of the manufacturers that is represented here today, I can tell you that most manufacturers send a warranty card in the package and request that each of the people who will end up with a glucose meter fill out the warranty card. It is both for manufacturing traceability but also for marketing purposes. The percent return of those cards is not 100 percent so manufacturers do know a lot of the customers but it is not a 100 percent response on those cards.

DR. NIPPER: Anybody else on the panel with questions for Ms. Trautman at this point?

MS. TRAUTMAN: Is there anyone who might want to think about what design controls are and how design controls may play into, when I looked at the guidance document that Mr. Gutman had provided, there is a lot of aspects of specificity and so forth that are really truly approval issues but also now starting June 1997, will be tied to the quality system regulation in the fact that manufacturers have to have a controlled system for designing their product, they have to have a design and development plan,

they have to establish their design inputs and in order to establish their design inputs, they need to gather inputs from a variety of sources, including user needs in the patients that they are going to be taking this to.

After they have their inputs, of course the engineers take and have these general specifications or requirements and start translating them into engineering specs or into the appropriate specificity specifications for the product. Then they are going to be required to do what we call design verification. Design verification is actually testing to make sure that the output of that reagent is actually giving the results that they thought was going to happen in the design input.

Beyond verification tests, the new regulation requires what we call design validation. Design validation basically is an additional step on top of design verification where manufacturers have to insure that they are meeting the intended use and the user needs for that product so there needs to be some sort of what we call clinical evaluation. Clinical evaluation should not be confused with full blown clinical trials. Clinical evaluation can be clinical trials. It can be non-significant risk IRB studies. It can be the fact that many a

manufacturer has a surgical suite or has a home environment for this particular product set up. They may ask some users to come in and play an test with the product and actually view and see if the person can follow the instructions properly and so forth.

So this requirement under design controls for design validation really is an additional test to make sure that the user needs and patient uses are really being attended to. When we teach the concept of the difference between verification and validation, verification is saying, okay, I have made all these assumption up front in my design input that I know, when I go and originally develop a product, this is what I want to develop. But there is still a lot of assumptions made there so verification only says I am making what I thought I was making.

Now, design validation is saying am I really making what I need to be making to satisfy my customers. Yes, sir.

DR. REJ: This is very interesting and relevant to this panel. Do you have copies of the quality system regulation here available for the panel?

MS. TRAUTMAN: We can provide you with copies.

DR. REJ: Is it on your web site?

MS. TRAUTMAN: Yes, it is, but we could also provide you hard copies as well.

DR. REJ: Okay, and in the design, the matter before the panel today are self-monitoring glucose devices and clearly the manufacturers have to have some semblance of a home environment to test out such a product. What about the end use of these products in a very, very different setting like in a hospital? Would it be required then for the manufacturers to also do that type of testing, validation and controls for the different environments for the use of the product.

MS. TRAUTMAN: Yes, it would. If the manufacturer knows that this product may be used in multiple settings, then the requirement require him to test that in the appropriate settings that he knows it will be used in. Now, of course, there are some times that a manufacturer may never know how a product may be used once it gets out on the market but if he does know that his product will be used both in a clinical setting as well as a home environment, then he needs to be able to show that that validation has accounted for both situations.

DR. BOUGHMAN: Joann Boughman, University of Maryland. That was actually something that slightly

concerned me in a document that we have before us on page eight where they were talking about physician's offices, laboratories and so on if this is to be used in hospitals, it would have to be tested at three different hospitals but, in fact, it seems to me the way the paragraph at the top of page eight is written that those devices intended for home use only have to be tested at the manufacturing site.

DR. TARPLEY: But according to this regulation, then, even if it was only at the manufacturing site, they would have to do some sort of simulated use testing or some sort of clinical evaluation and the next speaker, when they talk about human factors, the only real way to do that is to have users sit down and use it and to really meet the intent of the quality system requirement you don't want to pick someone who is a professional in this area and who knows it all by heart.

To truly test and do design validation, they should pick a typical or a normal adult or whoever would be using this in the home environment and ask them to sit down with the labelling, with the instructions and actually see and interact what type of problems may occur. Is the result or is the readings that you can compare to easily understandable and where there are confusions and where

there are problems, these should all be caught way up in the design phase so that if possible or where appropriate they should be changing that up in the design of the product even before they start manufacturing and before it is ever distributed.

DR. BOUGHMAN: Okay, thank you.

DR. NIPPER: Well, I think that the red light is blinking up there and unless there is a last, pressing question from the panel, I think that we would like to keep you here as long as your employer will allow you to stay so we can completely interact because I think we are beginning to get the flavor for what, how this document is going to be used and it is really helpful to have your discussion. Thank you very much.

MS. TRAUTMAN: Thank you.

DR. NIPPER: Okay, our next presentation dealing with human factors is by Ron Kaye. Is Ron here? Yes, he is. He is a human factors specialty with the Division of User Programs and System Analysis, Office of Health Industry Programs and the Center for Devices and Radiological Health. Mr. Kaye. That little light up there should switch to green eventually.

**Agenda Item: FDA Presentation - Human Factors**

**Issues - Ron Kaye, M.A.**

MR. KAYE: Okay. Mr. Chairman, distinguished panel members, ladies and gentlemen of the audience. My name is Ron Kaye and I have been asked to discuss human factors in invasive self-monitoring blood glucose systems.

As an overview, in this talk I will present its purpose, I will discuss the human factors perspective on use error with self-monitoring blood glucose systems. I will talk about and clarify use error as it pertains to these devices. I will briefly discuss some findings from selected studies that pertain to human factors and the use error for self-monitoring blood glucose systems.

I will present some strategies for reducing use error and finally i will present the summary and conclusions.

The purpose of this presentation is to maintain and focus awareness of the panel on human factors perspectives when considering the overall safety of self-monitoring blood glucose systems and stimulate continued thought on this topic.

I would like to talk a little about the subject of human factors itself. Human factors is often misunderstood or at least understood in different ways by different

people. This is mostly true because there is a persistent tendency to blame errors involving technology on the user. In fact, users often tend to blame themselves.

Also, the term human factors can mean different things which is confusing.

So what are these multiple meanings of human factors? For one thing, human factors are characteristics of people. These characteristics include abilities and behaviors that influence how people use technology. Human factors also are characteristics of the technology including design, the design concept and the costs that affect how that technology is used by people.

Human factors is the scientific discipline body of knowledge and technique that is applied to the study of how people interact with technology. Human factors is also the activity of applying human factors techniques, analyses, or data-gathering to improve systems that involve technology and people as in doing a human factors evaluation.

So what is the human factors perspective on use error in self-monitoring blood glucose systems? Inaccurate glucose measurements can result from flaws in self-monitoring blood glucose monitors or their accessories. They can also result from users not knowing how or not being

able to use self-monitoring blood glucose systems or their accessories to obtain accurate measurements. This presentation concerns itself with the problems or "use errors" that result only from the second cause of inaccurate glucose measurements are mentioned here on this slide. That is, use error as discussed here does not correspond to operational failure of devices.

To clarify this, let's consider a hypothetical situation in which a well-intentioned user uses a precise, accurate and fully operational device. With this user and device system, you would expect accurate output. If the output, in fact, is not accurate, use error has occurred. The cause or causes of this use error are human factors of the user and/or the meter and its accessories. I must say that I was very happy to hear Dr. Clement's comment yesterday stating that we must consider the user as part of the system and I couldn't agree more with that statement.

So what are the human factors that cause use error? On a very general level, use error can be expected when users experience difficulty using a device due to cognitive, perceptual or motor limitations on the part of the user. The use error can also be expected when users may not be aware that they are using devices or accessories

incorrectly.

Finally, use error can be expected when users may not be aware that the accuracy of the device has been affected, perhaps by external influences such as temperature, humidity or by blood hematocrit levels.

Why is consideration of use error important? Use error can and does cause harm to self-monitoring blood glucose system users when decisions on how to maintain blood glucose are based on meter output that does not reflect actual blood glucose levels. Patterns of use error may indicate that the device design, training, labelling, or any combination of these may be inappropriate for users.

If you review literature on this subject, you will find that several different terms are often used in reference to self-monitoring blood glucose systems for what is being called use error in this discussion. These include user error, human error, procedural error and poor judgment.

The term use error is preferable to these other terms because it is not beneficial to consistently blame users for errors or lack of good judgment. To invoke the idea that human error is always unavoidable, or to label errors as procedural when users may, in fact, be unable to perform procedures.

Use error is notoriously difficult to identify and understand. This may be true in part because it is difficult to test the accuracy of self-monitoring blood glucose system meters under realistic use conditions as we have been discussing. For one reason, when observed, users will perform differently and there is also the possibility of inadvertent coaching or instruction during any kind of observation or data collection.

Also, use error is most likely underreported and when it is reported, the information supplied is often limited as we discussed following Sharon's presentation yesterday. Use error scenarios are not well understood and finally the clinical significance of use error is not well understood.

The Food and Drug Administration continues to receive many reports of problems with self-monitoring blood glucose systems. Known or suspected causes of errors include meter maintenance, incorrect techniques or operating procedures, failure to follow instructions, use of expired or split test strips, use of strips incompatible with meters, environmental factors including temperature, humidity or altitude, extreme levels of blood components such as hematocrit and lack of or inadequate user training.

I would like to talk about some findings and conclusions of selected studies for those of you who may be following along in the handout, I think the pages may be slightly reversed. I am talking about the Jovanovic-Peterson page which may be the next page for you. I am not sure.

Studies that pertained to this topic include an interesting study that appeared in Diabetes Care in 1988 by Jovanovic-Peterson et al. This study was called "Identifying Sources of Air in Self-Monitoring Blood Glucose." The rationale for their study, and I won't get into the results of that study, but the rationale for their study was interesting. The authors stated that although previous studies of glucose oxidase strips have found them to be precise and accurate, few studies have been performed in the real world of patient use.

In 1990, the Department of Health and Human Services sponsored or rather it was completed in 1990, a study called "Human Factors in Self-Monitoring of Blood Glucose." In this study, the accuracy of results was found to be influenced by factors including meter familiarity to the user, ambient temperature, meter cleanliness, and the use of split test strips.

Whereby the percentage of observed readings produced by study subjects deviated more than 20 percent from baseline referenced measures are shown in the corresponding percentages and in this case, ambient temperature interestingly had the largest impact.

It is our understanding at the FDA that industry has taken steps to respond to these concerns and, of course, we are talking about a technology that has changed in the ensuing seven or eight years since the study was done.

The American Diabetes Association Panel Conferences in 1986 and 1993 included some interesting statements that correspond to human factors concerns for the use of these devices. The 1986 conference concluded that future systems should be simpler and less dependent on user skill. This statement was also reiterated in the 1993 conference.

Also in 1993, from the 1993 conference, was the statements that systems should be easy to use by children and people with decreased vision, impaired manual dexterity or other special needs. As we know, one or more of these concerns often apply to users of self-monitoring blood glucose systems.

The 1993 panel also stated that better methods are

needed to detect and prevent analytic user and sample collection errors.

Taking equity reports from 1994 and 1996 together, they made some interesting statements. They said that problems related to use error commonly occur with blood glucose monitors. They said that calibration and cleaning of monitors is often ignored. They suggested in that incorrect test strip storage and improper user technique contributes to erroneous results and they recommended that the competency of users be evaluated periodically.

Discussing the strategies for minimizing use error, near term FDA objectives as we just discussed in the previous talk, include that reasoned good manufacturing requirements which will soon become mandatory. These include a design input requirement which reads, "Each Manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient."

Another GMP requirement concerns design validation. This states design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or

simulated use conditions.

Among other suggestions, the 1993 National Steering Committee for Quality Assurance in Capillary Blood Glucose Monitoring made three recommendations that are pertinent to use error and human factors.

The 1993 Steering Committee recommendations included a recommendation to establish a task force to determine the clinical significance of use error. They said user error. I inserted use error. And to analyze factors that could contribute to clinically significant procedural errors and inaccurate test results.

Another recommendation was to establish uniform guidelines for training users or verifying their skill and finally to increase patient access to training and education.

Summary and conclusions. First, I would like to say that inaccurate glucose measurements can result from flaws in the self-monitoring blood glucose monitors or their accessories but these problems are not use errors as discussed in this presentation. In some cases, self-monitoring blood glucose systems may be accurate, precise and fully operational, the results are inaccurate in the hands of users. This is use error as discussed here.

Patterns of use error may indicate the device, design, training, labelling or any combination of these may be inappropriate for users. Identification of use error will consider characteristics of users as well as characteristics of devices. It is difficult to test the use of self-monitoring blood glucose devices under realistic situations.

Please bear in mind that user error with self-monitoring blood glucose systems is very likely underreported and not well understood. And, finally, regulatory manufacturing and user communities should monitor, understand, and take steps to reduce use error with self-monitoring blood glucose devices. I appreciate your attention. Please let me know if you have any questions or comments on this topic. Thank you.

DR. NIPPER: Thank you very much. I am sure we will come back to you many times today in our deliberations. Are there any questions from the panel briefly for Mr. Kaye at this time? Hearing none, thank you very much. We are running just a little late because we got a little bit of a late start but I still would like to do our best to keep on track as the clock allows us to do now.

We are about to move to an open public session.

During this session, we are going to hear perspectives on the manufacture of SMBG meters. There are speakers who are public attendees that have contacted the executive secretary prior to the meeting. These speakers will address the panel and present information relative to the, relevant to the agenda and the speakers are asked to state whether or not they have any financial involvement with manufacturers of any products being discussed or with their competitors.

The order of presentation as I have been given it today include the first presenter is Ken Ervin from Life Scan. Is Mr. Ervin present? We will reset the little traffic light for you up here and you have got 15 minutes. If you finish early, we will ask you a few embarrassing questions if we can.

**Agenda Item: Open Public Session - Ken Ervin**

MR. ERVIN: Good morning, distinguished members of the panel and ladies and gentlemen of the audience. My name is Ken Ervin. I am director of technical support at Life Scan. I have been there for nearly 14 years now so I have seen a lot of change in the glucose monitoring business.

My objective this morning is to try and convey a perspective from the manufacturers' point of view regarding the performance capability of glucose monitors and in terms

of the current technology and then to suggest that the DCCT may have already taught us what is actually required in terms of that performance.

I think as a preface it is fair to say that this is an intensely competitive industry and as such that competition is going to continue to drive improvements in the technology leading to better accuracy and, as mentioned earlier, reduction of use error. I think everybody recognizes the benefit of glucose monitoring but not everybody recognizes the challenge that this presents to manufacturers.

I am going to try to give a little perspective here. There are an estimated five million meters at this point in time. And during 1997, we estimate that something on the order of two billion tests are going to be performed in the United States. Imagine the possible combinations here with any given product. What we are saying is that any strip from literally thousands of strip lots can be used in any meter of which there may be a million or more of a particular brand and we are asking that product to be accurate over a very broad range of conditions. This is an immense task. It is an awesome task for the manufacturers to try and accomplish.

As we have seen, clinical performances generally assess by comparison to some reference method often a laboratory method and it is often shown using the error grid as we saw yesterday.

The error grid as we recall is based on a premise that an error of plus or minus 20 percent was clinically accurate. Now, that error grid as we remember from yesterday is from 1985. As far as manufacturers are concerned, we want our products in the A region. We are not making products or products that provide results in the B and C and D and E regions are not our target. Our specifications, our design and our process controls are intended to provide results within the A region.

However, when we look at that A region, we are talking about a term which I will call total error. I will come back to that in a moment.

When we look at the lower end of this scatter plot called the error grid, manufacturers are targeting that region I have indicated on this graph that Dr. Ratner used yesterday which shows a constant error from approximately 75 milligrams as far down as the meter will read. What we have found and what the current technology will provide is essentially a constant error at that point. We do not speak

in terms of percentage at that point because as you go to lower and lower glucose values, percentages become absurd so we speak in terms of an error of plus or minus 15 milligrams which is equivalent to 20 percent at 75. That is what we are targeting with specification and process control.

DR. NIPPER: Excuse me. The previous slide was taken off before I finished reading the bottom, and I am wondering if that was a two-standard deviation phrase that you are talking about.

MR. ERVIN: That is correct, and I am coming back to it.

DR. NIPPER: Thank you. I apologize for the interruption.

MR. ERVIN: I spoke in terms of total error. Remember, we are talking, we expect these millions of meters and billions of test strips to fall within that A region and we have to define this in some statistical term. We are using total error which is intended to encompass a number of variables and it does, essentially represent 95 percent of all data that we expect to see with a given system.

So let's take a look at what does, what we have to include in that. I have already mentioned meter to meter and strip lot to strip lot. Remember there is also within-

lot variability. In blood glucose monitoring, we are working with a blood sample which is inherently more variable than plasma samples that get used in the laboratory in that we have to deal with hematocrit variation as well as such things as PO2 and, of course, endogenous and exogenous interfering, potentially interfering substances and medications.

We have to do this with a neat sample, meaning we do not get to dilute it. In the laboratory they are able to dilute samples which assist in establishing a more uniform test medium. We have to contend with environmental variations, temperature, humidity, and altitude. Furthermore, we have to contend with variations in sample volume and the method and timing and such in its application. The design of these products is intended to minimize all of these variables and their impact on the result but they do contribute to some variability.

In spite of these many variables, we believe current technology is capable of delivering a total error of plus or minus 20 percent and in my own personal experience I have been told by many clinicians that they routinely observe better than that but I would also say that there are institutions, for example which are capable of exerting some

control over the user, that is through patient education and training.

My comparison, laboratory glucose results are performed under very well controlled conditions and they get to use the more uniform serum or plasma sample and even so, results will vary by as much as five percent and on occasion I have seen it as high as ten percent.

We just heard a presentation on use error. Remember I said earlier that manufacturers are interested in illuminating error that falls outside of the A region so our efforts over the years have been focused on such things as simpler procedures, finding ways to instruct the user through the device, through the use of icons or word instruction on the display.

We have focused on trying to provide technology that can operate with much smaller samples and to provide error messages if they do not apply the correct volume of sample. And in recent versions of products there has been a great deal of focus on error messages for other potential use error.

What I would like to do now is shift a little bit to the DCCT and I think it is fair to say that when that study began, people were using what we now call first

generation products. These were products with a fair amount of user influence on the test result involving blood removal, timing and those factors. Towards the end of this study, products of the second generation, eliminating those procedural steps began to be used and those products, when used correctly, were capable of providing results within 20 percent of reference values.

The results of the study itself, that intensive therapy with IDDM delays the progression and slows the onset of clinically important retinopathy, nephropathy and neuropathy are well known. There was, however, a downside.

It was also noted that the incidence of hypoglycemia was approximately three times higher in the intensive therapy group. However, overall, long term complications were reduced by up to 60 percent and I point out that the self-monitoring blood glucose technology was a key tool but only part of what was involved here in terms of diabetes management practices that made these improvements possible.

As I mentioned earlier, the industry is going to continue to strive for more accurate and reliable results. Competition is going to drive that. However, the question that really needs to be addressed here is not whether we can

make the products much more accurate but rather how we can improve its accessibility and applicability to achieving quality patient outcomes. Unless we would suggest and I think we have heard comments previously that are consistent with this, that the best leverage point for improving patient outcomes involves addressing the obstacles in the health care delivery system that prevent the broad deployment of effective diabetes management practices.

For example, patient education and access to that, physician and pharmacist education, diet and behavior modification, frequent testing. In the DCCT, one of the main differences between the intensive therapy cohort and the control group was frequent visit with the physician which provides for surveillance of their proper use of the monitors, reinforcement, all the factors that tend to keep the patient involved in doing things correctly. And, of course, intensive therapy.

Those are my comments and I am willing to accept questions.

DR. NIPPER: Thanks. We have a couple minutes for questions if there are any. Dr. Harrison Falls, please?

DR. HARRINGTON FALLS: I appreciate, this is Beverly Harrington Falls, I appreciate your very excellent

presentation and do have a couple of questions regarding the variation. You had said that sometimes the lab would have five, up to ten percent variation.

MR. ERVIN: That is correct.

DR. HARRINGTON FALLS: What are you basing that on?

MR. ERVIN: Person experience.

DR. HARRINGTON FALLS: Evaluation of a single sample?

MR. ERVIN: As director of technical support at Life Scan, when we receive complaints regarding inaccuracy, we investigate those complaints and part of that is to understand if there could be something systematic that might be contributing to error that we can address with design or labelling, so forth. Over the years, I have done many such investigations and I have seen in many situations differences on the order of five to ten percent between laboratory instruments within a given institution.

DR. HARRINGTON FALLS: So the variation was actually between different instruments?

MR. ERVIN: That is correct. There is also some variation within a given instrument and that probably is best indicated through such things as the CAP surveys. They

give you a measure of the standard deviation within the given instrument type.

DR. HARRINGTON FALLS: The other comment I wanted to make was in talking about use error this morning it seems that patient expectations is one of the factors that needs to be included although instruments and the technology are continuing to become more accurate. If a patient realizes in particular in a self-monitoring blood glucose device, that it is not necessarily a gold standard although it is aiming for that but it is just a way of monitoring between health care contact so that appropriate adjustments might be made, then the public would have a better understanding of what the goal of using these home monitoring devices is.

DR. NIPPER: Thank you, Dr. Rej?

DR. REJ: Thank you for the presentation. You just mentioned in your comments a follow-up on complaints from users of your product. Can you give this panel a sense on how frequently you hear from your folks in a negative way? We saw a very impassioned video tape yesterday and this panel on other occasions has heard presentations by diabetics and the sense that I got is they are very dissatisfied with the products they are using, or at least those that have come to this panel and that was made clear

in yesterday's video tape and now I am hearing quite a different story from the purveyors of these products and I am just curious. I mean, do you get one call a day, do you get 1,000 calls a day?

MR. ERVIN: We get many calls a day. I can't tell you the exact number but by far the largest number of them have to do with inquiries regarding availability, where they can purchase product.

DR. REJ: No, but I mean that the user sensed that there was a problem with the result, either that it didn't match the way they felt, it didn't match a laboratory result like we heard yesterday in the video tape or the same meter apparently agreed and didn't agree with a clinical laboratory result and the sense that at least I as a member of this panel have gotten from the actual users of it, much of this might be related to the use errors we just heard about. I am just curious as to what, to get a quantitative feel for it. I think that is what this panel was trying to do yesterday with the data from the FDA reporting system. This is also a little bit anecdotal but I would like to get a handle on the magnitude of the problem.

MR. ERVIN: I can't specify because I don't know what the total number of inquiries might be regarding

we call them accuracy complaints. However, what we find in follow-up investigation is that there are misunderstandings in terms of what the user expects. A common example would be the monitors that provide a whole blood result and that result now has been compared to a plasma value from the laboratory and sometimes without control for fed state. In other words, we are dealing with capillary venous differences and the huge majority in probably nearly all the cases, these are resolved over the phone with the customer.

If there are instances where there may be something, product is returned, they are provided with new products and that product is investigated inside the company, in situations in dealing with hospitals if there appears to be something that could be systematic rather than associated with a particular device, manufacturers will send representatives to study the issue and that is where my experience comes from. I have, over the years, visited maybe a dozen hospitals where there were issues associated with performance. In every case it was resolved and in many of those it was issues around calibration. Calibration within the individual laboratory which is kind of a disappointing thing to have to say but that is what I found.

DR. NIPPER: Dr. Goldsmith asked me to be next.

DR. GOLDSMITH: Thank you. I had a question. You raised the issue before that of more than five million glucose meters are out there. Do you have any idea how many of those are home use, hospital use, maybe by home health care company, used by nurses, et cetera.

MR. ERVIN: I am sorry, I really can't address that for you but I would suspect that the vast majority are in home use.

DR. GOLDSMITH: And one other question really. Why do you think manufacturers can't product monitors that are reliable lower than 75 milligrams per DL?

DR. ZAWADZKI: The problem with the low glucose range, well, first of all, I am not sure I could, I completely agree with the statement that they are not reliable if I understood your question correctly. The question is, what is the error that the technology is capable of staying within in that region?

When you are dealing with a very small signal and you have all of these other influences as I mentioned, temperature, sample volume, humidity, there is basically a variability that is inherent in the technologies that we cannot avoid and that is what becomes the limiting item when you are talking about very low glucose values because there

is just not very much signal to measure there.

DR. NIPPER: Dr. Zawadzki?

DR. ZAWADZKI: Thank you. I have two questions. The first one is how is, what is the actual process within the meter by which a sample is standardized to give a result in terms of a plasma or a whole blood reading?

MR. ERVIN: You are referring to the calibration process for the monitors I presume. Okay.

DR. ZAWADZKI: And the actual final output of a given meter.

MR. ERVIN: Right. Meters and strips are designed as a system and I think that is an important thing to get out here. Manufacturers have designed these as systems. Strips and meters must work together.

In that calibration process, what is done is we measure the response of the system, that is, a combination of meters and test strips and then calibrate the test strips with application of a calibration code that causes that response to be identical to some reference device. Many of the manufacturers use a YSI as their reference device. Other manufacturers may use other approaches. So we have a methodology that is a reference and we have to have a sample then that becomes the reference.

In the case of YSI, we can choose. We can use whole blood as the sample in the YSI or we can use plasma. What we are doing is setting the monitor to provide a result identical to some reference and it is arbitrary as to which we can use. Initially, all the manufacturers used whole blood as the sample. Many of them used YSI as the methodology.

More recently, largely stimulated by the fact that users were confronted with trying to understand why whole blood and plasma do not read the same, manufacturers have moved to providing calibration to plasma. And in that all we are doing instead of using the whole blood sample is we now use a plasma sample in that reference methodology. Plasma sample, however, is from this same blood that was applied to the monitor in measuring the monitor system's response.

Does that help?

DR. ZAWADZKI: I have one other question. How many of the inserts for the different meters actually recommend comparing the meter result to a glucose value, a simultaneous glucose value obtained at the doctor's office by laboratory method?

MR. ERVIN: I don't have the answer to that. I do

know that in terms of our communication with customers, primarily through the customer service, the 800 line, that is a very heavy recommendation that there is the frequent reinforcement of accuracy of their devices with the health care professionals.

DR. NIPPER: At this point, in the interest of time, I would like to put a halt to the questions. I am assuming you will stay here so that we can continue to ask other questions as they come up during the panel.

MR. ERVIN: That is correct.

DR. NIPPER: Thank you very much, Mr. Ervin. Our next presentation is by Biocontrol Technology. I have three names. Is this going to be a trio or is it going to be a one, two, three? Who is going to be first?

MR. PURDY: I will be one, two, three and I am first.

DR. NIPPER: And you are Patrick Cooper?

MR. PURDY: No, I am David Purdy.

DR. NIPPER: You are Mr. David Purdy, okay, and you will introduce your co-workers when the time comes.

MR. PURDY: Yes, I will.

DR. NIPPER: Thanks very much.

**Agenda Item: Biocontrol Technology - Mr. David**

**Purdy**

MR. PURDY: Thank you very much, Dr. Nipper. I appreciate again the opportunity to address this panel again. I am David Purdy, president of Biocontrol Technology. With me today is Dr. Thomas Pitts who is an endocrinologist from Chicago and is a member of our medical advisory board. Also with me is Dr. Patrick Cooper who is Biocontrol Technology's manager of applications engineering.

My corporation, Biocontrol Technology, Inc., has been intensely involved in the development of a non-invasive glucose sensor since 1986. At the present time, we are conducting a clinical home use trial of the production model of the diosensor 1000, non-invasive glucose sensor and are cooperating with Dr. Gutman and his staff at the Food and Drug Administration. Scientifically, the diosensor 1000 is an automated diffuse transfectanse infrared spectrophotometer. The spectrophotometer measures the amount of light absorbed by different materials.

The diosensor 1000 detects the absorbance of glucose from infrared light transflected from a patient's arm. It uses analytical chemistry methods developed within the new field of chemometrics. These computational analysis techniques are used to relate the measured glucose to the

infrared spectra, thereby providing a mathematical relationship between the spectra and glucose concentration allowing the meter to read out the glucose reading in a liquid crystal display.

At the present level of our technology we feel that the non-invasive device has a place in patient care but that is not yet a total replacement for the fingerprick glucose sensors represented by other manufacturers here. We believe for certain patients, the non-invasive device can effectively complement the use of conventional devices.

Our proposed use of this device has been patterned to provide safety for a certain class of patients and utilizes the advantages of both conventional and non-invasive therapy. We calibrate the device to each patient but the patient would not use the Disensor 1000 until the device has successfully measured glucose for a certain period of time after the device has been calibrated.

Our calibration centers would participate in education of the patients for whom the device can be calibrated and for the physicians who oversee their care. We have also instituted a quality assurance program to be used by the patient in the home for which the patient tests with a conventional, well-performing conventional device and

compares it to the non-invasive device three times per week. The patient would also be required to return to the calibration center periodically to check the device performance.

In this manner, safety for the patient is assured. The patient will not receive a device unless the measurement process for him or her is successful. The diosensor 1000 has also been designed so that a control sample is tested before each reading. This control sample has a spectral absorbance comparable to that of human skin and contains 100 milligrams per deciliter of glucose.

If the control sample cannot be measured accurately by the device before each measurement, the liquid crystal display will inform the patient that the device is out of calibration. This is an example of a feature that is not present in present-day, conventional fingerprick glucose sensors.

The diosensor 1000 will also indicate an error that goes not detect a spectral signal strong enough to give an accurate glucose reading. It can also sense errors in placement of the arm such as movement. Dirt, contamination of the probe if the probe has not been properly cleaned or if the skin should be obscured by clothing.

Key to the utilization of this technology is the fact that the patient to device interface, in aerospace terms, the man-machine interface, unlike conventional fingerprick glucometers, it is very simple. The patient merely places his arm and punches a button. He is not required to draw blood, to accurately position blood droplets in target sites or strips or any of the other problems that have been indicated earlier today.

The diosensor 1000 is the first device which can measure glucose non-invasively. It is analogous to the first fingerprick devices 15 or so years ago. All of us have seen the improvements and progress which have been made using these devices and they have been remarkable. The same standard for devices which have been commercially used for 15 to 20 years should not be used, in our opinion, to measure new, non-invasive technology which, like all devices, has its advantages and its disadvantages. These advantages and disadvantages are different than those displayed by conventional technology and thus should not be evaluated by the same criteria.

We feel that clinical relevancy and usefulness of this device should be determined by the prescribing physician, not by a statistical or numerical standard that

has little clinical relevancy.

At this time, we are cooperating on a daily basis with Dr. Steven Gutman and his staff at the Food and Drug Administration. It is our sincere hope that by this joint cooperation by our corporation and by our regulators that we can both achieve a place in patient care for non-invasive glucose detection.

I would now like to introduce Dr. Thomas Pitts who will discuss the relationship between actual patient management and the performance of home use blood glucose monitors. Thank you.

**Agenda Item: Thomas Pitts**

DR. PITTS: Thank you for the opportunity to speak today. I am going to address clinical concerns regarding patient directed glucose monitoring from the standpoint of an endocrinologist.

I have been in practice and supporting tight control of diabetes or intensive therapy as has been mentioned earlier for about 16 years. I practice in a large metropolitan area of Chicago, both in a university setting and have another office in a small community on the south side of Chicago.

I have also been supporting a number of diabetes

related educational and legislative goals and I am kind of involved in this process in a lot of different areas.

I am here today in part as a consultant for Bico(?), the spectrophotometry technology for non-invasive glucose measuring and clearly in support of that. I would like to say that I began as a fellow and a past president of the American Diabetes Association's lab, Norbert Frankel, taking care of pregnant diabetic women in the late 1970s and early 1980s.

We began glucose monitoring about 1980 with large, bulky, frequently inaccurate glucose meters that required wiping of fingers as well as test strips, so-called wet technology as a part of capillary glucose monitoring. Needless to say, the accuracy of many of our patients was less than optimal with large errors being reported frequently.

Still, even at that time, we were able to use the information to advise modest changes in insulin or diet by looking at a series of comparable tests over several days to achieve better plasma glucose and hemoglobin A1C values. Since that time, as Mr. Ervin has mentioned, the meters have become much less expensive and the techniques have been much less demanding. Still, old habits are hard to die and I

find myself still looking at a series of values over time to better judge or gain insight as to glucose excursions and insulin needs.

Hypoglycemia remains a relative frontier, potentially more dangerous than significantly elevated or hyperosmolar glucose values. In my practice, even with more accurate capillary glucose determinations of the current technology, I generally treat symptoms and I treat trends more than specific values. In that sense, I am less dependent upon the accuracy of even the current technology that we have talked about, having significant problems in the hypoglycemic range.

Because of the different risk for hypoglycemia and the complications I have been able to successfully do that, again achieving significantly improved hemoglobin A1C values in a broad spectrum of patients with a broad spectrum of incomes and ability to purchase glucose capillary strips. I think we talked about human error. Clearly splitting strips is not an educational issue but clearly that is an economic issue.

Because of these problems, it becomes necessary to also for physicians like myself to make judgments as to who can have tight control. That is to say, who comes to the

fore with the relative insight and judgment and other people, other things to support so that we make those decisions as to who can effectively be benefitted by this kind of technology, who can be benefitted by intensive therapy and who, in fact, would be perhaps more harmed by that. I think that remains the physician prerogative and shall do so in the future.

In summary, most decisions to improve diabetic control are made based on insights gained over repetitive testing, looking for patterns of glucose exclusion and in that sense, whether a meter is accurate on a particular value or not or less so is the repetitive values that we use to make these kinds of decisions. In fact, for the most part, in any judgment decision, one specific value has quantitatively less significant point. We look, in general, as I said, for tendencies or patterns and I think until we find the technology that closes the loop, that will continue to be.

So I guess my point is that we should, to some extent, for both the non-invasive and invasive technology, I find that for the last 16 years, it has helped me improve hemoglobin A1Cs and according to the DCCT, that is associated with a better outcome, even with its current

technology. I wasn't here yesterday and I did not hear or see the informative video by a specific patient and I should say that those problems occur but for the great majority, they gain more than they lose.

A question was asked, how many meters are being used in homes. Back in 1980, less than one percent and those people had to pay for those meters with their own money, often costing upwards of \$1,500. I should say as a private endocrinologist, I have about 70 percent of my practice of concerning people with diabetes are now using meters at various levels. The improved technology in terms of being more a friendly user has helped considerably. The more things we can do to help that will be useful.

The one clinical situation that has not been mentioned but has been talked about is the fact of how busy peoples' lives are who have diabetes and that is to say they are not eating specifically at certain times because their work and their other responsibilities are cooperating. They have a lot of issues. They don't live specifically for diabetes but diabetes is one of the issues.

Until we are able to really help people control that in terms of all the other issues and racing to get through a test so they can race to get to something else, we

are going to have a certain amount of error that continues. Again, repetitive testing in the current technology for invasive and really sort of the same for non-invasive in the sense that non-invasive technology will encourage, if anything, more repetitive testing, more frequent data collection, more data collection, will be useful.

I will take any questions after our third speaker. Our next speaker is Mr. Patrick Cooper with Biocontrol. Thank you.

**Agenda Item: Patrick Cooper**

MR. COOPER: Since my responsibilities for our company encompass both clinical and regulatory affairs, I would like to address issues related to the testing and review of new technologies. Earlier, Mr. Purdy asked that clinical relevancy is the deciding factor in whether a device should be allowed to serve the needs of the diabetic community. Of course, clinical relevancy must be established through appropriate clinical testing. However, it is equally important that device reviews consider data in light of the device's intended use which may be different for new technology and which, therefore, may allow different standards of performance.

Device reviews must also consider the relative risks and rewards offered by new technology which may be used by a patients now currently using existing technologies or which may provide additional information to physicians or other caregivers.

These general issues can probably be better understood by considering the case of a company's non-invasive device. As a company attempting to obtain approval for the first non-invasive blood glucose monitor, our device has certainly come under considerable scrutiny. There has been both praise and criticism. We modestly accept the praise.

Much of the criticism, while often well-intentioned, has been misguided. For example, we do not disagree that an inaccurate test result may be more dangerous than no test result at all for some patients. But it has been reported that up to 60 percent of patients with insulin dependent diabetes mellitus and 74 percent of patients with insulin treated non-insulin dependent diabetes mellitus do not monitor their blood glucose at least once per day. This represents at least as many as one and a half million people with diabetes, not monitoring their blood glucose at least once per day. These are all people that

use insulin.

However, these are patients who do not usually adjust their insulin dose unless specifically directed by their physician to do so. Perhaps with these patients the low frequency of self-monitoring may be more dangerous in the long term than a few inaccurate test results. An often overlooked area for a new technology is its application to patients who cannot be served by existing technology. Current blood glucose monitors, even those equipped with voice modules and which may be otherwise specially modified cannot always be effectively used by patients who are visually impaired or who exhibit diminished motor skills without assistance.

A non-invasive device equipped with a voice module could at least provide a means for these patients to self-monitor blood glucose where currently available alternative devices are decidedly deficient.

Finally, the needs and interests of the patient are paramount. If there is any subset of patients for whom a device can be demonstrated to be clinically useful, then that device should be tested and reviewed accordingly so that those patients' needs and interests can be served and let us not forget the needs and interests of the physicians

who treat these patients. If a device can assist the physician in improving patient outcomes, or even in continuing the current level of care, then the physician's needs and interests should also be considered since they are ultimately those of the patients.

For example, please consider that a small subset of patients does not monitor blood glucose at all and a larger subset monitors less frequently than desired due to the pain and discomfort of finger sticks. According to a recent study, poor metabolic control was associated with the performance of fewer self-monitored blood glucose measurements per day and that this relationship was mediated by the fear of blood and injury.

Certainly, a device which requires physician involvement in its distribution and use and which would be appropriately and clearly labelled provides a means for accommodating these patients without compromising their safety.

On behalf of Mr. Purdy, Dr. Pitts, and Biocontrol Technology and Diosense, Inc., I thank the panel and the FDA for the opportunity to address this group. Thank you very much.

DR. NIPPER: Thank you. I am going to call a

break at 9:45 according to what our agenda is. We have two or three minutes. Are there questions from the panel for the presenters that have just come through? Ms. Rosenthal?

MS. ROSENTHAL: This question is for David Purdy. David, you mentioned that you recommend calibrating three times a week and in between, how is the device used? Exactly what are the mechanics of calibrating it?

MR. PURDY: The mechanics, possibly I might have not made it clear enough because we were a bit rushed but we calibrate over a two day period and then we follow the patient for another period, we recalibrate. This is the continuation of the calibration period and then we watch the patient for a period which we call verification. If the device performs successfully then they would be given the device to take home or rather they would be given the device to use. They would actually do, take the device home and do the calibration at home with another device.

Now, once they are using the device, the quality control procedure is the time that we do it three times a week. As a quality control procedure, we ask that they use a conventional finger prick glucometer three times a week and compare it to the reading they are getting from the D-1000 and that is a quality control procedure to assure that

that device remains in calibration.

MS. ROSENTHAL: And between those times they use that device alone.

MR. PURDY: Pardon me?

MS. ROSENTHAL: Between the times that they are comparing, they use that device alone as you would use a glucometer.

MR. PURDY: Yes, yes, they would use it normally, yes.

MS. ROSENTHAL: Thank you.

MR. PURDY: You are welcome.

DR. NIPPER: Are there any other questions or comment? Dr. Rej.

DR. REJ: In your quality control procedures, you are asking the individuals who would use your product to use it in comparison with a conventional, one of the invasive glucose meters, correct?

MR. PURDY: Yes.

DR. REJ: What sort of criteria are you recommending or do you anticipate recommending to the users for what would be a successful agreement and what would be an unsuccessful agreement?

MR. PURDY: The purpose of our clinical trial at

the present time is to determine that exact correlation. What we are doing is we are conducting a clinical trial working with, as I mentioned, the Food and Drug Administration, and during that trial we are determining an equivalency between conventional, fingerprick glucometers and the Diosensor 1000. When we have analyzed that data, then we would be able to come up with the criteria that would allow us to assure that both treatments are equivalent.

DR. NIPPER: Dr. Harrington Falls. That will be the last question.

DR. HARRINGTON FALLS: Also regarding your calibration of each device, in the situation such as the video we saw yesterday where there were multiple children in a family, there is one device per person or is the software capable of calibrating for each person?

MR. PURDY: The Diosensor 1000 has a PC-MCIA card in it and the patient's algorithm, which is the mathematical equation that computes the actual performance of the patient and the device and gives the reading, that algorithm is stored on the PC-MCIA card so in case of the mother who has the two children that you saw yesterday, we would calibrate both children separately and they both would have their own

PC-MCIA card. When one of the children, when her daughter used the PC-MCIA card, she would insert the PC-MCIA card. When her son used the device, he would insert his PC-MCIA card. We can calibrate up to 10 or 15 patients in one but we did it mainly for that very reason, to serve a family who are diabetics.

DR. HARRINGTON FALLS: Thank you.

MR. PURDY: Sure.

DR. NIPPER: Thank you. I would like to thank the FDA presenters this morning as well as the commercial presenters. We will reconvene promptly at 10:00 to hear other manufacturers and health industry representatives.

(Brief recess.)

DR. NIPPER: If we can all take our seats please and let's take off our makeup and acting faces and bright lights and cameras and the little red wagon are gone. We can relax and we can scratch and yawn again. I would like to welcome you back to the clinical chemistry and toxicology devices panel meeting. We are in the midst of an open public session. I would like to remind presenters again to tell us if they have a financial involvement with manufacturers or products being discussed or with their competitors. That is a requirement that I joyfully ask you

to do because we would like to know where you are coming from.

The next speaker says she is from the Health Industry Manufacturers Association and Roseanne Savol. There you are. Fire it up, Roseanne, and let's go.

**Agenda Item: Roseanne Savol**

MS. SAVOL: Okay. Thank you, Dr. Nipper. My name is Roseanne Savol and I am the manager of regulatory affairs for Bayer Corporation and I am from Elkhart, Indiana. I am here to represent the Health Industry Manufacturers Association and to lead off a series of presentations on blood glucose monitors and the self-monitoring of blood glucose. What I would like to briefly cover with you this morning is to go over some of the technological developments in the blood glucose monitoring industry, the labelling developments that go along with the meters and the reagent strips, the human factors engineering activities that the industry has been involved with over the last 15 to 20 years and the collaborative efforts that the Health Industry Manufacturers Association, the manufacturers of the equipment and the community, the diabetes community, has participated in over this almost 20 years of concentrated available self-monitoring of blood glucose.

Yesterday, Dr. Gutman gave a presentation and went over some of the historical development of blood glucose monitoring technology. For those of you who weren't here yesterday, I would like to recap that a little bit.

Fortunately, I am very pleased to say that blood glucose or let's say monitoring capabilities for diabetics predates lots of us. I think that is really nice to know that it is not that new within our lifetime.

Actually, it was in the 1940s that the tests for reducing sugars in urine first became available as reagent tablets. In the 1950s, the tests for glucose in urine, the reagent strips became available. At that time there was also a test for blood glucose as a reagent tablet that was available. Later on in the 1960s, the tests for blood glucose as a reagent strip appeared. In the 1970s, the meters and in the 1980s, the meter and reagent systems that were specifically targeted for the self-monitoring of blood glucose.

I thought I would bring some pictures if some of us haven't seen these before. For example, in 1941, Miles put out the first diagnostics with the clinitest urine sugar analysis kit. Later on, in the 1950s, there is a, the reagent strips for urine sugar and right next to that is

dextra-test which is a test for blood sugar that also appeared in the 1950s.

The we flash forward to the 1980s when the self-monitoring systems became available and also for those of you who haven't seen some of the -- Dr. Habig, do you want to pass this around to the panel -- these are the blood glucose meters that first appeared in the 1970s that were used to monitor diabetics. And then, of course, we have seen these developed later on into the 1980s and now almost everyone is familiar with the meters and the strips that are so tiny and are like the size of a credit card.

Along with the technology developments over the last 50 years, 50-some years, the accessories, the components of the testing system developed also and labelling developments really became part of the industry's activities as the self-monitoring devices became more available and so the, within the collaboration of the Food and Drug Administration, the industry, the HEMA members and the professionals, there were several guidelines that developed during this period of time.

Yesterday it was pointed out that the FDA put out its points to consider guidance for the review of home tests and largely at that time, blood glucose testing devices,

pregnancy testing devices, ovulation and whatever, were the principal home use tests that were available. Right around that time also the National Committee for Clinical Laboratory Standards started to have a consensus development process for a voluntary consensus standard for the labelling of home use products and that was proposed in a standard form in 1989 and it came to its approval process last year in 1996.

Then concurrently or overlapping with that, the Food and Drug Administration put out a guidance manual that is Write it Right. It is a recommendation that the FDA put together for user instruction manuals for medical devices used in home health care and this broadens the concepts of good labelling materials, instructions for use, beyond just the home tests but this also has application to other types of medical devices that are used in home health care like glucose monitoring systems being a device use in home health care.

Human factors engineering is a term that has become more familiar over this period of time and as Mr. Kaye said earlier, as blood glucose systems became more available and more used and the practice of blood glucose monitoring became more used, the FDA sponsored a contract

for a study on the human factors analysis of blood glucose monitoring. This contract was completed 8/1989 or 1990 and he went over some of the conclusion of that study. A fallout from the human factors study was another collaborative effort. It was called the National Steering Committee for Quality Assurance in Capillary Glucose Monitoring that was developed in 1990 and that went through 1993 and there were some several ADA consensus conferences that fell out along this line from this type of activity.

In the area of human factors engineering, I think this is a nice depiction of some of the human factors innovations that the blood glucose monitoring industry has implemented during this period. As you can see, one of the, from 1996 now down through 1997 as each generation and model of system comes to the market, there have been things that have been developed such as the reduction in calibration strips or steps compared to what was done in some of the earlier systems, display readability was improved, the ergonomics of holding things. Everyone now at work is up to here with ergonomics. We have ergonomic sessions, ergonomics training. This is just within the office setting but a lot of this has been involved in the development of products for quite a long time now and then efforts to

minimize the environmental effects, increase memory capacity and these little meters, it is amazing the amount of memory capacity they have been able to squeeze in as the developments, as the models have been improved.

And then also the improved resistance to electromagnetic interference.

In the area of reagent strips that go along with the systems, technology has continuous been able to use less and less blood sample. The test timing has been reduced. The effects of common interfering substances have become reduced and the resistance of environmental factors because of the packaging, the humidity and whatever, has been improved and some systems allow some sample reapplications so that helps the user and the protection of the reagent area in the manufacturing of that has also been developed.

In part of this human factors engineering process, the services that manufacturers provide has also developed to a large extent over the last 15, 20, 17 years. Twenty-four hour customer support systems are available at times. The customer support for toll free numbers are common, almost a must-have for almost anyone working with home users. The training programs for new users are greatly supported and materials are provided and developed. Multi-

lingual customer service is available.

The educational materials that manufacturers provide to the clinical, the practitioners, the nurse practitioners and the health providers that support the systems are available and the data management systems. There are capabilities of transmitting blood glucose results over phone lines through models to health providers in remote areas and that has been available I would think probably well over 10 years.

Part of this diabetes management control and everything is a community effort. It is one thing I have learned in my 25 years working with blood glucose monitoring systems is that the diabetes is a community effort. It includes the health providers, the manufacturers, the health care agencies and the diabetes, persons with diabetes themselves and their families. I would wager that for every diabetic, that diabetic represents at least four to five people in their immediate, that have touched with their immediate lives so it is not just the diabetes community, it is not just the individuals with diabetes and their immediate health care providers. It encompasses a much larger community and manufacturers have always been involved in this.

The National Steering Committee that I talked to you, mentioned before, was developed out of the human factors specific science and engineering study of the mid-1980s and the steering committee met and I think in 1990, out here at the National Institute of Medicine. It encompassed government agencies, people from universities, developers of technology, professional organizations and the manufacturers of the blood glucose systems at the time.

The work product of the National Steering Committee was resulted in several recommendations that were published in diabetes care and there were, this group proposed strategies for the future development of self-monitoring of blood glucose and the care of persons with diabetes and one of the, out of this, the proposed strategies were recommended that research be done to document the clinical significance of procedural errors associated with monitoring. The development of consensus guidelines for training of the health care professionals who assist in the diabetes management and the lay users and that, you have seen that that is developing on an ongoing basis.

And one of the recommendations is to increase the access to training and education. I think yesterday the

diabetes educator also mentioned this as one of the important goals in the diabetes community is to increase the access and the ability for an individual with diabetes to come and have the availability of having them be tested on a regular basis.

Out of this consensus group, the National Steering Committee, one thing that the manufacturers took on at the recommendation of the steering committee was to emphasize and re-emphasize and continuously emphasize the need for training and assistance in performing blood glucose monitoring. One of the things that the manufacturers did agree to is a labelling statement that you can see in the labelling of the systems. This is a warning, an advice to potential users because people do buy several different types of meters. It is not necessarily one on one. Sometimes people have them at work, at school, some for taking on hiking and camping, that before using any product to test the blood sugar that it is important to read all the instructions for each system and to do all the quality control checks that are recommended and that this recommendation applies to all blood glucose monitoring systems and was supported by the American Diabetes Association, the American Association of Diabetes Educators,

the Food and Drug Administration participated in this and the Health Industry Manufacturers Association.

On behalf of the Health Industry Manufacturers Association I am real pleased to be able to give you this little overview of the history of blood glucose monitoring and we are committed as an association of manufacturers to continue to work with the Food and Drug Administration and the rest of the diabetes community to continue this, the steps for further improvements into the future. I will be willing to answer any questions you might have.

DR. NIPPER: Since it is 10:20, we will hold questions until we get the next block of speakers done. Thank you. The next speaker is Donald Parker. Dr. Parker is from the Bayer Corporation in Elkhart, Indiana, and I think you are going to use experiences, too.

**Agenda Item: Donald Parker**

DR. PARKER: My name is Don Parker. As Dr. Nipper said, I am director clinical trials and clinical research at Bayer Corporation and relative to my association, I am directly associated with a manufacturer of blood glucose monitors. It is with great astonishment and glee I go every other Friday to pick up a paycheck so I have to admit that I have no regrets about that at all.

I want to talk to you for just a few minutes today about blood glucose monitors and some issues that I have in my own mind that are weighing heavily on my mind with respect to performance guidelines and evaluation expectations for these meters and I am going to talk to you briefly about the following items. One, what some of the so-called standards of practices are today, what some of the key issues are for blood glucose monitors. I want to talk a little bit about the published evaluations, the quality of those evaluations. And the impact that they have on the reputation of glucose monitors and its utility.

And then I want to talk a little bit about laboratory method accuracy, particularly using some proficiency testing data and some data which we collected in the last six months relative to the traceability of laboratory methods to the CDC, the National Reference for Clinical Laboratory Sciences system for the deprogrammed plasma, hexokinase reference method and then make, draw a few conclusions for you.

Just to review them, many of these standards of practice have been discussed the last few days, yesterday and today, so I won't have to go into great detail. One that we talk about a little bit are the proficiency testing

goals in CLIA within plus or minus 10 percent and consistent with Mr. Erwin's conversation, you get down to the low end and we talk about a concentration rather than a percentage but these are the goals associated with the CLIA process for proficiency testing and they do impact on judgments that are made in the clinical laboratory.

DR. NIPPER: Dr. Parker, are those two standard deviation or one standard deviation?

DR. PARKER: Those are, I think those are the variabilities. They are probably two standard deviation points bias but they are at least two standard deviation.

The 1986 consensus conference that has been discussed here in great detail, particularly with reference to the fact that in the range of 30 to 400 milligram per deciliter, it is expected that the system variability would be less than 10 percent 100 percent of the time and this system variability is approximately the two standard deviations again or 2 CVs. An acceptable range of performance would be plus or minus 15 percent of target.

Then the 1993 consensus conference, shooting for a much more rigorous goal, analytical error goal of five percent and Dr. Gutman, I think very clearly presented the relative level of confusion about what that analytical error

might be, whether it is total error or CV or but it is under any circumstance a very rigorous goal, a goal that many of the glucose manufacturers, meter manufacturers are dealing with today, particularly in Europe. The TNO guidelines are another guideline that you might be interested in seeing. They are looking at plus or minus 15 percent of the target glucose above approximately 100 milligram per deciliter using a hexokinase glucose method and using capillary blood comparisons and then below the 6.5 or 117 milligram per deciliter target, they are using approximately plus or minus 18 milligrams so that is the European standard that seems to be getting a great deal of use.

One that is brought to the fore and we are using to some degree these days because it is a consensus document and it is the NCCLS C-30 approved document which is the ancillary glucose testing document and it calls for within 20 percent of the laboratory result above 100 and within 15 milligram per deciliter below 100.

With respect to performance goals and also with respect to clinical goals, the error grid analysis of Cox and Clarke that was discussed yesterday also provides us something of a reference at concentrations greater than 70 milligrams per deciliter plus or minus 20 percent and less

than 20 percent is expected that if both the meter and lab are there then there is an area where you need to think about beginning to respond and that any association is acceptable but I think Mr. Ervin pointed out quite correctly that that is a bit broad from an analytical point of view.

The other thing I would mention to you is that Leroux, et al., Leroux and Setia published about two years ago an error grid analysis for hypoglycemic specimens in the range of 0 to about 160 and they put much more stringent standards at the low end of the scale and give you more guidelines to work with and if you are not looking at that, I would suggest that that would be worth looking at less than 30 milligram per deciliter treatments obviously are required. If both systems are below that, and so no analytical concentration would be essential above 30 milligrams. They are working at approximately plus or minus 11 milligram per deciliter spreading out a little bit more as the concentrations rise but in the range of about 70 to 100 plus or minus 11 milligrams per deciliter.

When you are looking at blood glucose meters, there are a number of issue that we have to deal with when you do an evaluation or when you do a consideration of what acceptable performance is with these systems and each of

these has to be considered. It has to be carefully balanced. You have to take their issues and design those into your evaluation or you will come up with an evaluation that will not give you an acceptable answer. It is my personal opinion that probably close to 40 or 50 percent of the published papers on blood glucose monitors are fundamentally flawed and the data useless.

And it is because the people designed experiments to answer the questions that they are interested in and the way they want the question answered and that is an unfortunate fact from my point of view. But with respect to glucose monitors you have to look at strip chemistry because on the market now there are four major strip chemistries out there. There are glucose oxidase peroxidase with color indicators, the glucose oxidase with electrochemical indicator, the hexokinase and the glucose dehydrogenase chemistries. You have to take in mind what is the membrane or matrix that the material is absorbed to because the flow characteristics into that and the way it reacts several different ways can have a significant impact in performance comparisons.

You need to look at the individual meter use characteristics. You need to consider the sample.

Yesterday I think Dr. Gutman mentioned capillary of the venous samples but we are also getting great and greater demand for use of these things with arterial specimens and it brings, because of the oxygen content and a couple of other factors, other serious considerations to your evaluation. Whether you are going to report whole blood or plasma results, what sort of system have you used to calibrate it, whether it is the YSI or hexokinase procedure or glucose dehydrogenase procedure where they are using plasma or whole blood samples as part of your calibration matrix.

Control materials, a tremendous problem because of the technology issues of delivering whole blood samples to the market. You just simply can't do it in a reasonable way. There are a number of control materials that are on the market. Four blood glucose meters. They all have tremendous matrix effects and so you have to be cognizant of that. And then the difficulty, the lack of a viable reference method and the user technique issues.

In the publications themselves, there a number of publications that I think have been very positive contributors. For instance, the Giordano publication was a joke to us but they basically told us you need to pay

attention to altitude. If you don't pay attention to altitude, you could report incorrect results. Although it may be a negative event from our point of view, it warned us of something we needed to deal with and that we are working to do with.

The NMN paper, this last year with use of evaluation of hypoglycemia, an interesting approach to doing that, a very nice evaluation by Harrison et al providing a number of different ways to look at blood glucose monitor data statistically and that the Aiken paper, for instance, you all know this is the paper that published the data that clearly demonstrated to us the problems associated with using blood glucose meters in people who are severely hypotensive or who have poor peripheral blood circulation and so a good contribution to the clinical side of the picture.

One publication I wanted to mention to you because it has been so visible the last three or four months, a publication in Diabetes Care in December by Tragenosky(?) et al., and they looked at six different meters and did a comparative evaluation and their basic conclusions are here. One is that the stringent criteria of the 1990s or 1988 consensus conference were not met by any of the blood

glucose monitors and I would have to agree with that and the availability exceeded not only the five percent in 1993 goal but in most cases the 15 percent total error and the 10 percent variability goals of the 1986 conference.

Using the Clarke error grid analysis, they felt that some of the results fell into clinically unacceptable zones. The reason I mention this paper is because there are several key failures and these failures were first used with an inappropriate specimen. They used arterialized venous whole bloods. The people were on a hyperglycemic, hyper, or excuse me, hypoglycemic, hyperinsulinemic clamp for several hours and the samples were collected from a hand catheter in a 60 degree centigrade box and the hand was in the box for several hours, ostensibly to profuse blood more effectively into the samples. It was a more capillary-like sample but the result is you get a sample that is somewhat elevated in temperature and somewhat changed in characteristics from the normal sample.

There were venous samples and two of the meters used in the studies do not use venous samples. They had a good hospital comparative method but at no time did they try to characterize the bias of that method compared to some reference or some standard material. The result was I think

some very incorrect data and they used some, I think some very good interesting statistical techniques but used it with incorrect data.

And they relied heavily on correlation coefficients in the area of 40 to 80 milligrams per deciliter and got some, I think some incorrect conclusions from that and then used the Clarke error grid analysis which is totally insensitive in that end or that concentration when they could have gone to something like the Leroux error grid and made a meaningful estimate of clinical performance.

I just provide this slide to show the correlation with the scatter plots that were published in the paper and I think if you, I know the board has to hand out but if you will look at that, you will see that the results are scattered reasonably well around the X equal Y line in all cases and considering it is the low concentration area, probably a pretty remarkable performance in the hands of the nuclear people who don't normally do blood glucose monitoring.

One of the things I wanted to point out is the reason I got into this is that this particular plot is the regression plot for one of the meters and the blue line is the lower limit of detection of that meter. You will notice

circled there are five data points which the meter cannot report. And this was missed by a series of I think probably scientifically excellent reviewers but I think this is not atypical of some of the publications we see and these results would have a significant impact on any conclusion you draw about this study.

Well, I am not naive enough to think that they would make mistakes only on this meter. It is clear to me that there is bad data for all of the meters and just to give you an example, here were some of their other statistics and for that particular meter, since I know that meter and its performance characteristics, they are basically saying that 4.2 percent of the results were greater than 40 percent of the reference method. Well, 4.2 is five results, 4.2 percent is five results. These five results are not reportable. They are not real results.

By the time I get through, here is a paper that is very well accepted. It is very widely publicized. It has fundamentally flawed data that discredits two or three of these meters inappropriately.

Then there were some error grid analysis issues, and I think if you were to use the Leroux error grid analysis which is specifically designed for hypoglycemia, a

completely different set of conclusions for all of the meters.

And then the methods of residuals are inappropriate, probably for all of them but certainly for one of the meters. And the reason that I do this, this article has been the full employment act for Don Parker. I have now written seven letters to the editor to seven different journals on this article. And so it is the reason I bring it to your attention. I know it has been on the Reuters News Service on the Internet, various interest groups, it has been in Diabetes Care, Diagnostics Intelligence, the New England Journal of Medicine, Clinical Laboratory News for the AACC and Diabetes Interview. I don't know how many more.

But it has been an interesting effort. And in all but the original paper, people have summarize the data. Diagnostics Intelligence, for instance, summarized the data this way. They put the names of the meters and I just put letters but they put the correlation coefficient, the percent of results less than 20 percent of target and the percent of results greater than 40 but they made their conclusions about acceptability on the correlation coefficient and one of the meters they say is excellent had

6.6 percent of its results greater than 40 percent and only 46 percent within 20 percent.

So very poor conclusions on very poor statistics. If you look at proficiency testing data, what it can do is I wanted to point out the impact that laboratory methods can have on our results. These are data from a major proficiency testing program for three of the samples and I have the all-methods material, glucose oxidase electrochemical, glucose oxidase peroxidase and two hexokinase procedures. These are the mean biases that you see and these are large laboratory systems that are used by hundreds of laboratories in every case.

What you see is the biases on these range from minus 2.5 to plus 6.7 percent, a 9.2 percent variation in bias in the mean result with large laboratory methods. The last slide of data that I want to show you is these are some of the data that I have collected in clinical trials in the last six months. When we do a clinical trial, we take six materials out. These are controlled materials. They are frozen human plasma that has not been treated in any way other than to freeze it but it has been spiked with glucose to give us these concentrations. What we do with these materials is we take the CDC reference method and we do a

full protocol to determine to the best degree we can what the target value of that material is and then over the life of the use of that, we do one measurement per month just to confirm the stability of that material from month to month.

We send them to all of our investigators and we have them do 10 duplicate measurements there before they start and one duplicate measurement per week during the course of the clinical trial. And these are the data that we came up with. You can see we cover the range fairly well that we need to look at and these methods across the top are different laboratory methods. A-1 and A-3 are two systems from the same manufacturer at two different sites. And you will see that the variation differs by as much as three percent for that one manufacturer.

B-1 and B-2, two systems from two different manufacturers at two different sites and these systems compare pretty well although they do run up to about 2, 2.5 percent bias, mean bias difference. And C-3 and C-4 are two of four sites that used one specific instrument and we provided all the reagents so they had all the same lot of material and you can see these two major systems differ by as much as six percent at the different sites.

I point out sites D and E and I have put them in

the same column because my Power Point will only give me eight columns. I was delimited but I figured I got sneaky here. D is the top value, E is the bottom but if you look across here, you see that method D and method E vary by as much as 15 to 16 percent in mean result with methods that are, with specimens that are traceable to the CDC reference method.

These kinds of issues are issues that we deal with on a day to day basis and anyone in a laboratory who evaluates a glucose monitor has an obligation to make sure they understand what the bias of their reference method is.

Basically in conclusion, the following one is consensus on blood glucose monitoring accuracy really is not available what our needs are and that is one thing we need. We need a clear understanding of what blood glucose monitoring capabilities are and where they are going to be used.

We need scientifically and clinically sound evaluations of blood glucose monitoring systems and it is my opinion that this doesn't often happen. We need to be sure we use these things consistent with their intended uses. We need to adhere to use recommendations. We need sound experimental design and data analysis which I know this is

what the FDA is calling for and then we need clear and appropriate guidances and regulations relative to what these systems are and how they are applied and we need to pay particular attention to the reference method because for whole blood glucose we do not have a reference method.

What we are doing is when we do it, we are going back to the CDC, deproteinized plasma, hexokinase method and using that as a reference method so we are indirectly standardizing our system on a plasma basis so this is a difficulty for us and then I put a plea for all of the scientific community to pay more attention to the review of this literature and the appropriate scientific rigor.

Thank you very much.

DR. NIPPER: Thank you, Dr. Parker. In the interest of trying to maintain our schedule, I would like to move along to the next presenter who, according to my list is Edward Kimmelman from, I am sorry, it is Glenn Pittluck from Medicines Incorporated. I am sorry if I give anybody heart failure. It is Glenn Pittluck from Medicines Incorporated in Waltham, Massachusetts and I believe Mr. Pittluck is approaching the podium.

**Agenda Item: Glenn Pittluck, Medicines Incorporated**

MR. PITTLUCK: You didn't give me a heart attack but you might have given Ed one.

Good morning. My name is Glenn Pittluck. I am the director of quality assurance and regulatory affairs for Medicines Incorporated, now of Bedford, Massachusetts. We have moved.

We are a manufacturer of self-monitoring blood glucose systems. First of all I would like to thank you all for the opportunity to speak this morning. I have just a couple of brief comments regarding the medical device reporting of self-monitoring blood glucose systems.

Several times yesterday, the question of the number of self-monitoring blood glucose tests being performed was raised. HEMA, on whose behalf I am speaker today, was able to obtain information about this from four major manufacturers of test strips including Bayer, Thoringer(?), Life Scan, and Medicines. Just to give people a sense of the number of tests being performed, this partial data indicates that in 1994, 2.5 billion tests were shipped worldwide. In 1995, 3.15 billion tests and in 1996, 3.57 billion tests were shipped. Again, this data is only four of the manufacturers.

Based upon information obtained through the FDA's

web site which we checked again as of Tuesday of this week and we noticed that Sharon had some more updated information on 1996, we were able to obtain the numbers for 1994 and 1995 and compare them to the number of strips being shipped and this comparison identifies that the rate of adverse events reported throughout the MDR system is 1 per 2.8 million tests shipped in 1994 and 3.1 or excuse me, 1 per 3.1 million tests shipped in 1995.

Now, none of the manufacturers want to see any adverse effects or adverse events and we don't want to give the impression that we enjoy these. We certainly don't but the numbers are really quite low.

Yesterday, Sharon Dillard discussed some of the limitations of the MDR system. One of the limitations Sharon pointed out is that the allegations in an MDR need not be confirmed to require reporting by the manufacturer. This is true and is supported by the following quote from the MDR regulation as published in the Federal Register December 11, 1995. The FDA, this is a quote, FDA also disagrees with comments stating that reporting should be required only when a device directly causes an adverse event or is a significant factor. Section 519-A-1 and B-1-A of the Act requires reporting of any adverse event when

information reasonably suggests that a marketed device may have caused or contributed to a reportable event. Limiting reporting to adverse events directly or significantly caused by devices would narrow the statutory reporting standard which requires reporting of adverse events when a device may have caused or contributed to an adverse event. End quote.

So again, the implication is through a phone call to a complaint system and we need to investigate all of these and if there is a mention of an adverse event and it is associated through the call to self-monitoring blood glucose tests, we are obligated to report this to the FDA, regardless of whether it was a causative factor or relationship, we are obligated to report it and we do that. The manufacturers all have systems to evaluate all of their complaints and report those events which fit this criteria.

In summary, the limitations to the MDR system do exist and we acknowledge them and again the shipment rate are approximately three to four billion strips per year over the last three years and the incidence rates are approximately one per million strips shipped so I am going to help you get back on schedule and say that is the end of my comments and if you have any questions, I can entertain them.

DR. NIPPER: Thank you. We do have time for a question or two from the panel if there are any. Seeing none, thank you very much for the time and now we will invite Ed Kimmelman from Boehringer Mannheim to address the panel. There is a preponderance of Hoosiers on this list today.

**Agenda Item: Ed Kimmelman, Boehringer Mannheim Corporation**

MR. KIMMELMAN: I will take this opportunity to thank Sharon and Steve and the panel for allowing me to make this presentation on the current DCLD submissions guidance related to self-monitoring glucose products. I will try to be brief and for those of you who know me, you realize that that is quite a challenge.

I will not step my way through the current guidance document commenting section by section. I will refer to sections as I try to make points and illustrate them.

Over the years, FDA management has publicly stated that FDA submissions guidances must remain fluid. They must be able to quickly reflect the advances in technology and the new things that FDA reviewers learn about products. I

agree with that position. If there are safety and effectiveness issues that represent a significant general public health problem, in my opinion that doesn't appear to be the case here. As a result we are left with a situation where fluid guidance leads to delays in getting these products cleared for sale and all the negative effects that result from those delays.

In my years of work within NCCLS and ISO, I have gotten a fine appreciation of the benefits of broad and balance input to standards and guidelines. I know some of you on this panel have worked well within those organizations and may share this appreciation. On February 27 of this year, in response to a citizen's petition filed by the Indiana Medical Advice Manufacturer's Council and the expressed interest of Congressman Dave McIntosh, FDA published in the Federal Register its new policy on the use of good guidance practices in the development of guidances like the one we are considering today.

Consistent with that policy, the management of DCLD is holding this meeting to gather information and has promised to hold additional meetings for the same purpose in the near future. We in industry are relying on that promise and look forward to participating in those future meetings.

During this presentation I will be addressing the points shown in this overhead. I will not read them. I will give you a moment to look at that.

The key criterion manufacturers use in determining the effectiveness of submissions guidance is the extent to which that guidance results in facilitated review and expedited decision making by the agency. If an individual guidance document doesn't have that beneficial effect, it is of little use to the manufacturer. It is a frustrating and resource-wasting experience to present to the agency a submission that follows closely the published guidance only to find that the reviewer is using a different guidance document, one that hasn't been published yet or one that represents the individual reviewer's preferences.

That is why I am encouraged by the FDA policy on good guidance practices and look forward to its use in this situation. I believe it will be a good test case for the policy.

The objectives of each guidance document must be focused and clearly stated. If that focus is impaired by trying to cover too many different types of products, even though they may have a number of things in common, the agency should consider developing more than one guidance

document. DCLD has already recognized that fact by developing a separate guidance for the use of SMBG products in neonatal situations.

That same approach may be considered as the agency addresses invasive versus non-invasive systems, quantitative versus semi-quantitative or qualitative systems or generic strip products versus dedicated systems.

The current guidance document has grown like Topsy over the years and contains references to various types of systems with those references inserted sometimes in odd places resulting in confusion.

As I said before, the basic objective of these guidances should be to facilitate the effective and efficient review and decision making on premarket submissions. While this objective would result in some background information being included in the document, the current document appears to have a second objective, that of educating the reviewer who may not be familiar with SMBG systems.

I suggest that such educational information be included in a separate document or in an addendum to the guidance. Inclusion of it within the body of the document blurs the focus.

I also suggest that the history, background and information related to the various available methodologies be brought up to date with the inclusion of information on current systems. For instance, the human factors section of the guidance refers to studies conducted prior to the introduction of non-white test systems. Also, the software validation and verification section should reference current guidance document on these subjects. I am sure manufacturers would be happy to help DCLD develop an up to date educational document.

I suggest that to the extent possible the guidance be in the form of a parametric standard. A parametric standard is one that informs its readers of the issues that must be addressed, without being prescriptive about how they should be addressed and includes performance or design requirements only when such requirements are essential and generally accepted based on broad and balanced input. The labelling regulation contained in 21 CFR 809.10 is a good example of a parametric labelling standard.

The list of performance considerations within the current guidance document with some of the prescriptive verbiage related to the use of malamine to prevent glycolysis with that removed is another good example of a

parametric standard text.

I suggest the guidance document not be used to teach basic laboratory practice, especially if that information is already in locations that can be referenced. Much of the common interferences and delusion schemes information in the interferences study sections of the guidance document fall into this category.

Lastly, the guidance needs to be updated to include all significant reviewer requests for information. For example, our experience indicates that reviewers consistently ask for information related to the manufacturer's procedure for establishing reagent stability claims, yet there is nothing in the guidance to indicate that such information will be requested.

With the implementation of the new quality systems regulation which you heard about this morning, becoming effective in June of this year, FDA will have two bites at the design control level. It will have authority for the first time to routinely inspect the systems that manufacturers use for design control. In addition, it will have access to the premarket review process as it always has to the design of products that come out of these control design processes. Consideration of human factors is a key

element of satisfactory design control.

I suggest that it will be a worthwhile challenge for the product review side of FDA to coordinate better with the regulatory compliance side of the agency. That way, FDA can indicate in guidances which human factors considerations might be important for manufacturers to address and can be confident that manufacturers who are in good compliance standing with the agency have design control systems in place to determine if such situations are truly relevant to their products and to employ appropriate design control processes to translate those considerations into the final product.

Such an approach relieves the individual reviewer from the burden of determining the adequacy of individual human factors design decisions, a task which the reviewer may not be prepared to fulfill.

The current guidances tend to be overly prescriptive when discussing product performance. On page eight, for example, the guidance explains in detail the locations for precision testing and the numbers of lots to be involved. This detail leaves the impression that it applies to all cases and leaves little room for manufacturers to develop cost efficient alternative study

protocols. The specification of malamine as the apparently only agent for preventing glycolysis as I mentioned before is another good example of overly prescriptive language.

Another example of overly prescriptive language is on page 10 in the information related to consumer studies. The recommendation requires that results retained by the consumer and technician be masked from each other, even on systems that provide a test result that requires no interpretation by the tester. In that case, masking adds little value and may add cost to the study.

On the other hand, the language used on page eight related to hemoglobin studies is an example of good and useful guidance language. One additional small point. There should be language in the guidance to indicate that manufacturers should adapt referenced NCCLS standards when applying them to SMBG evaluations. Since many of these standards were developed to guide evaluations of large clinical laboratory systems, many of which use homogeneous and not use reagent systems.

The issue of quality control and any efforts to beef up the QC performed by the lay user must be dealt with in a pragmatic way, understanding the history of past efforts, the current performance of SMBG products and the

reasonably anticipated medical benefits and risks.

Manufacturers currently provide as part of the SMBG product and service offering a number of things that facilitate the use of controls. Two levels of controls are provided in most user kits and are usually available in separate packaging. In addition, controls are available, usually at no charge from telephone support units if a user is having problems that can be analyzed or corrected through the use of these control materials.

SMBG monitors have built-in controls to monitor their performance. QC instructions are provided in user friendly language in user manuals. As difficult as it is for those of us with scientific or medical backgrounds to swallow, the decision by the lay users to perform quality control is, to a great extent, a financial one.

If additional strips are provided at no cost to the user to perform QC, the user will likely use those strips for patient testing. If FDA required the design of strips or other reagent units to incorporate an automatic QC, it would likely increase the cost of those reagent units and might lead to decreased use by the tester, decreased testing.

In any case, the decision to move in the area of

QC is complex and it is complex enough to require thoughtful, broad and balanced input beyond that which can be achieved at this meeting alone.

To some extent, labelling targeted at lay users and labelling described in 21 CFR 809.10 is mutually exclusive. Targeted labelling should be easy to read and understandable by non-technical and possibly visually impaired people. Unfortunately, wording that is either required or anticipated by the labelling regulation is beyond the comprehension of many lay users.

In focus group testing conducted by my company, we found that generally required terms like reagent, in vitro and quantitative determination are not plain English. The same labelling concerns relate to some extent to the use of these products in POL situations. Unfortunately, much time is wasted during the submissions review process assuring that all requirements of 21 CFR 809.10 are met in the product insert even though all involved realize this information is not likely to be used.

As a result, we have a situation that cries out for DCLD leadership in getting the manufacturers to be comfortable with actually submitting to the DCLD targeted labelling in place of the classic insert sheet. DCLD has

already demonstrated that leadership in the area of OTC HCG test kits and other OTC blood tests. I encourage DCLD to do the same here.

Manufacturers are well on the way to completing detailed comments on the current guidance document. Unfortunately, there wasn't sufficient notice of this meeting to allow completion in time for the meeting. We intend to complete these comments and are willing to work closely with DCLD to develop any new guidances that seem appropriate within the context of the new FDA good guidance practices framework. Thank you very much.

DR. NIPPER: Thank you, Mr. Kimmelman. We have one other speaker this morning and according to my list, it is Paul Fox, Medical Devices Agency, Hannibal House, Elephant Castle, London, United Kingdom. Welcome, Mr. Fox.

**Agenda Item: Paul Fox**

MR. FOX: Thank you. Although in the manufacturer's section, another manufacturer per se or indeed a fool so I just want to thank the panel for letting me speak at this meeting and providing some perspective of how we do things in the UK but from the adverse incident side related to what we heard yesterday and the regulatory framework.

DR. NIPPER: And please tell us whether or not you have any financial interest since you are not from the mainland.

MR. FOX: I am just about to. I am going to put all these upside down back to front so if you will bear with me. Good morning. My name is Paul Fox. I am a senior medical device specialist from the United Kingdom's medical devices agency. We are part of the United Kingdom Department of Health and therefore I can confirm no financial interest in any manufacturer or any products which they produce that we have discussed today.

The medical devices agency is charged with promoting safe and effective use of medical devices used in the United Kingdom and until very recently, when I moved to the agency, I had been working as a clinical biochemist and I now have responsibility for in vitro diagnostic devices which includes self-monitoring blood glucose systems.

The prime reason for my attendance, therefore, is to learn, while I am on the learning curve, however, it was indicated to me that if I briefly went over the approach of the UK and Europe, now or over the next few years it might be of interest to both the panel and some of the attendees. It might be of no interest whatsoever but the fact I am

speaking helped to convince my boss to pay my fare over here so here we go. I genuinely hope it may be of interest.

The medical devices agency is essentially divided into three business units and I will do these in a slight different order to which they appear here. I will return to the European and regulatory affairs business related to finish. A brief word on device evaluation and publications.

This business controls a voluntary device evaluation program, the results of which are passed through to all device users within the National Health Service and outside and these device evaluations are used as an aid to purchasing decisions and quite a proportion of the device evaluations that are used within the clinical chemistry pathology section are on blood glucose meters. These are both comparative evaluations and single evaluations as new meters hit the market.

Device technology and safety is my section which includes the adverse incident reporting center. Now, in the light of the presentation, very interesting presentation yesterday of the details of the FDA's adverse incident data base, I thought it may be of interest to recount some of our experiences.

However, I must emphasize and I think you will

find the key word at the moment in the UK is voluntary. This is a voluntary system as with the device evaluation reporting. This evidences, therefore, probably less reliable even than the FDA's which I know was imperfect in many ways, post-market surveillance and should be treated as almost anecdotal.

There are a couple of things, though, that I think might be worth mentioning that we found to be different than those indicated yesterday. Firstly, our definition of an adverse incident differs somewhat although similar in many ways to the FDA's. We actually include in our adverse incident the potential for death, injury, et cetera. Now, I am not sure whether it is this. I suspect it is rather a reflection of a very different health care system but the proportion of adverse incident reports coming from health care professionals dramatically exceeds the figures indicated yesterday by the FDA.

I can't quantify that. As I said, this is almost anecdotal but we have a much higher level than that. I think it was seven percent quoted yesterday.

I think it is a relative point that we don't run away with the idea that these devices are performing exceptionally well in the hands of health care professionals

or perhaps more importantly that they are not performing to the standard expected of them by health care professionals and that is likely but certainly different I think.

Indeed, reports of poor performance of blood glucose meters by health care professionals have recently led to the medical devices agency to issue what we call a safety notice which had to remind the professional users of contraindications associated with blood glucose measurements and in a similar manner, these safety notices get passed throughout all users in the health service.

I was also interested to hear reported that adverse incidents initially ascribed to the user were likely found on investigation to be the fault of the meter. I would say our experience is completely opposite. As Dr. Ross I think indicated yesterday with respect to Selcore test strip errors, users tend to blame the technology first rather than look critically at their technique. I see many Ph.D.s in the background of the panel here and I am sure many of you have met students and technicians who have arrived saying a piece of equipment is malfunctioning or it doesn't work. You would like to find it is not even switched on.

I think the take-home message can be, if it can go

wrong, someone will probably find a way of doing it. We currently have a problem with an incident, again, very anecdotal, but with a blood glucose meter manufactured here in the states, programmable for use in multiple languages, got to the UK, programmed on English. Brilliant. The guy programs it, unfortunately programs on English is milligrams per deciliter and we use millimils per liter so in a perfectly functioning machine this guy has managed to grossly overestimate his blood glucose and inappropriately changes his medication.

So the meters often function very well per se but just are not used in an appropriate manner I think.

So to sum up our experience of adverse incidents, we see little evidence of a generic problem with a performance of the meters. Most problems seem to stem from inappropriate or incorrect use and I think as one panel member said yesterday, simple, simple, simple. I think that backs up what we heard earlier on use error or on user error as we tend to refer to it.

I think this simplicity of use is one reason where the manufacturers although have been moving forward, there are areas which continue to be addressed I think.

The health care professionals, and it is a dual

approach that we encourage, we certainly encourage various could address problems regarding to training and the proper use of the meters.

Okay, now, if I move away from adverse incidents slightly to what we have as a regulatory framework currently in place in the UK, that is pretty impressive and that is about it. There is some exaggeration there but not much. The only in vitro diagnostic related regulation in the United Kingdom are the HIV testing kits and services regulations which make it illegal to supply HIV testing without the involvement of a registered physician. And the other regulations are regulatory substances which obviously don't apply to self-monitoring of blood glucose and general product in health and safety regulations so I think you can find that more or less at the moment, if you make your meter, you can put it on the UK market.

One European regulation that doesn't appear there that is relevant at the moment and I will comment on European regulations briefly, is the electromagnetic compatibility directive. We have heard that these machines may suffer interference from electromagnetic sources and there is a European regulation relating to that.

This is due to change on a European scale. The new

approach directives of the European union aim to bring about the completion of the steel market by introducing harmonized and statutorily based controls to regulate the safety and marketing of products within the European union. Current directives in force refer to active implantable medical devices and medical devices generally but accepted from these and in a special group are the in vitro diagnostic medical devices.

These devices mean any device marketed must have a CE mark and there is a misprint in there. It is safe and fit for intended purpose. These directives for the in vitro diagnostic equipment are expected to be fully in force by about 2001. They are currently negotiating conclusions and I can guarantee it is a painfully slow process. At this point, the reporting system for adverse incidents will become compulsory and the data may improve somewhat and become less anecdotal.

The easiest, so to put your device on the market at this point you need a CE mark. The easiest but not the only way to achieve such a CE mark will be to comply with a relevant, voluntary harmonized European standards and the standards relating to the labelling of reagents and the easing of use of instructions for self-testing are currently

being rewritten.

The directive is likely to split products according to the risk of the patient should the product not perform in an inappropriate manner. That would be, probably those changes will be the European Union definition of an in vitro diagnostic medical device and you can see the reagents calibrate its controls, kits, instruments, more or less the whole shebang will require a separate CE mark. Blood glucose meters are likely to be in a sub-group which requires stronger regulatory control than most of the other IVDs, I mean, that definition takes on everything to blood sample tubes.

I suppose the good news for any manufacturers present is the CE mark will allow absolute unrestricted access to the markets of the European Union and the European Free Trade Association. However, probably less attractive will be the fact that any FDA approval per se will be irrelevant to the bodies which award these CE marks.

That is a very brief overview and I hope it was of interest. Thank you.

DR. NIPPER: Thank you very much. We have about 45 minutes for lunch. I would like briefly to take a stand-up and stretch break. I would like to come back at 11:30

and spend about a half an hour on questions for presenters that we had this morning and I would like to also review the five questions that the FDA has asked the panel to address so that we will be a little bit alert to what type of questions the chair will be asking panel members for this afternoon.

So let's reconvene at about 11:30, promptly at 11:30 for a real sprint toward the finish at 12:00, well, not the finish but lunch.

(Brief recess.)

DR. NIPPER: In the interest of allowing some of the people who need to catch a plane or go back to work at the FDA to escape, I would like to use this half hour to see if there were questions that arose during the presentation this morning. Before I do that, I would like to take the liberty to do two things. The first thing is that I would like to project scribble that I made during this morning presentations to help me get a handle on what we are actually talking about when we talk about 20 percent error or plus or minus two standard deviations.

Since I scribbled this, it may not be legible to people in the back room so I am going to walk out and try to read what I have done. A few years ago, there was a really

good paper about error in cholesterol measurements in clinical chemistry and Herden Ieto who was one of the authors described what the effect of various error ranges would be on measurements at the decision points with this wedge-shaped diagram like this.

So what I have done is on this X axis is plotted 100, 200, 300, 400, 500 milligrams per deciliter of sugar. Unfortunately for our colleague from the UK, I didn't do millimils per liter but it will be okay I think.

Now, the inside wedge is the plus or minus 20 percent, two standard deviation line so the effect there is to show you what the upper bound and the lower bound of the 95 percent confidence limits are at various levels. The outside wedge is not to scale, of course, because I couldn't do it on the piece of paper that I was scribbling on but that is the three standard deviation line which encompasses 99.7 percent of the observable measurements. Of course, there will be pooling of the data around the mean but I want, I think that the group, if you look at this wedge, can understand why there was some frustration on the part of our video taped mother yesterday because, you see, if the instrument is performing as appropriate at the 200 level, it is within performance specifications and does not imply a

use error to get a range between 160 and 240 as the read-out.

So it is perfectly understandable why two measurements in sequence on the same device would give us that wide a range. If you look at all the measurements, you are talking about 140 to 260 at the 200 level. I think that in consideration of whether or not in answering the question about do we have a problem, we need to keep in mind this type of wedge. You see, if we go out to 300, the range becomes 240 to 360 if my arithmetic done at the table is okay. Down at the lower end, I am sure it is going to be very hard to see my scribble. If you go with your plus or minus 15 milligrams per dl, at 70 it is going to be, at 75 it is going to be 80 to 60 at 50 it is going to be 65 to 35 which represents a wide range in hypoglycemia in my experience and could actually invoke two different medical responses.

And at a range of 25 would be 40 and 10. Again, a considerable range, even with the fixed amount. The question is, are we asking these devices to do too much, et cetera. But I think instead of talking in 20 percent plus or minus, it sometimes helps us to write down how wide the barn door is here and where we are saying it is acceptable.

If you think it is okay for self-monitoring blood glucose devices to read 160 to 240 on a 200 sample and be within specs and that no adverse effect can occur then we are okay. If you don't think it is acceptable and we can back that up with appropriate medical information, I think that is something we have to talk about as well.

So I thought I would draw this wedge for my own benefit and share it with you for whatever use it turns out to be.

I am going to leave the transparency projector on and the reason I am going to leave it on is that after we circle around for questions I would like to remind the panel and the audience of the questions we need to ask ourselves and respond to this afternoon when we go into open committee session.

Remembering now that we have heard from Kimberly Trautman and Ron Kaye from the FDA and several speakers, Ken Ervin and so forth, I won't name them all by name, I would like to go around the panel and see if there are any questions for those folks so in case they, that way they can remember what they, it is in proximity to their talk and maybe they can remember what they said and maybe we can remember what they said a little better.

Dr. Habig, do you have questions for anybody who spoke this morning?

DR. HABIG: The simple answer is no.

DR. NIPPER: Okay, and Ms. Rosenthal does not have any because she is not here. She is being video taped so we will hold her questions until after the make-up wears off. Dr. Harrington Falls?

DR. HARRINGTON FALLS: I didn't particularly have a question although Mr. Kimmelman might like to be available to provide some response. Regarding the guidance and how it tends to be fluid, there are so many variations in practice situations that for us to say this is how it should be is really going for a gold standard that a lot of practitioners might never utilize so there does have to be some fluidity in the guidances.

He had mentioned also that sometimes when a marketer will come before the panel, then they will end up with all these questions that they didn't anticipate and that is really a tribute to the excellent preparation because the major questions have all been answered so the panel then comes up with these exogenous questions. It is not our intention to give you a moving target to hit.

With Mr. Fox's presentation, I was just going to

mention since health care professionals in the UK do report more than United States physicians that possibly the FDA might consider coordinating with some of our training institutions because if we could just get the medical students in at the ground floor and say, here is the form. If you ever see adverse reaction you can send it in or report it. It will be very simple and you might notice the increase in the adverse reactions.

I have also been impressed by the fact that for many of our products, the 800 numbers that the manufacturers provide to the patients for follow-up is extremely helpful when the patient can call in, the main factory can get a large data pool that an individual practice or one city might not see and therefore they can address any issues that recur.

DR. NIPPER: Thank you. Dr. Clement?

DR. CLEMENT: Obviously I am still very fascinated as a clinician on the whole issue of non-invasive technology and also this question is addressed to Dr. Cooper and Dr. Pitts. I think one thing that this committee has been struggling with is first, where is the niche of these devices. I was impressed positively with the issue that your company is looking at it as a supplement to invasive

blood glucose monitoring and not as a substitute for that.

I think that has been very helpful.

And the other issue I think has got potential to go forward is this whole issue of well, if we can't show substantial equivalence and all these other issues based on number crunching and these standards that we show here, what was mentioned by yourself and Dr. Cooper was well, if it improves patient outcomes, obviously that is a benefit in the right direction that we want to go at.

In order to prove that in a scientific trial, it would be some pretty clever design methods actually to show that. Do you have any suggestions?

MR. PURDY: Well, we think we have a very unique design concept in our trial. The concept is really the concept that we have discussed at length with Dr. Gutman and his staff. We have come to the point and I don't want to speak for Dr. Gutman but some of that is proprietary because the sensitivity of our product in the press nowadays so we think we have an approach that will provide you with, as physicians, and this approach as we have six members on our medical advisory board of which Dr. Pitts is one, these are all, there are five endocrinologists and one internist. We are conducting the trials at the present time in two

locations and we have a large number of patients relative to what you may have remembered from our last meeting.

This trial has been designed so that we can show clinical relevancy in a comparison, a one on one comparison with glucose, finger prick sensors in the home. This to my knowledge is the first time that a manufacturer has been required, in spite of the many, many millions that are being spent on these devices to show that this device works in the home and I was pleased to see the comments that some of the people from the Food and Drug Administration made this morning on the possibility that by June of 1997, the FDA has instituted their quality systems program which allows and requires that the devices be tested in a realistic environment so the Food and Drug Administration will have more capability to get that kind of feedback and the issue really is very simple.

Most of my background is in aerospace and one of the big problems in the aerospace industry is the man-machine interface between the machine and the man and that is what was referred to here when they mentioned use, patient use or user error. We called it man-machine interface problems.

That is the main difference and that is the reason

wee feel that our device is essentially equivalent and we tried to explain that before using the error grid which, a you remember, was very controversial. And we didn't have enough patients and also we had not done a home trial. We are doing that. We have done everything this panel here recommended to our knowledge. We are doing everything that the Food and Drug Administration from Dr. Gutman to Dr. Albert to Dr. Burlington would like us to do. We are cooperating with them and I think that that will possibly lead the way to a methodology so the FDA incidentally are not allowing us to get around that issue. And they have asked us to present an approach which we have but I really have to say that it is proprietary.

I think, however, that the U.S. --

DR. NIPPER: May I interrupt at that point?

Excuse me. If this is, if the material you are asking for is germane to the subject matter at the end and you would like us to, we can clear the room and ask Mr. Purdy to present that information to the panel. We can do that.

MR. PURDY: I would be glad to do that if Dr. Gutman.

DR. NIPPER: I stand corrected, Mr. Purdy, I apologize. That is for a different venue. So forget that I

interrupted you but withdraw your remarks to close reasonably soon. We have others.

MR. PURDY: I am finished. Is that okay, Dr. Clement?

DR. CLEMENT: I guess for now but it would be more depending on the assumption.

DR. BOUGHMAN: Joann Boughman from the University of Maryland. I am not sure whether it is Ms. Trautman or Mr. Kaye or somebody else from the FDA that might help me out here a little bit but I understand in the total quality system process now on that side of the house, if you will, there is the pre-market now inspection and device development control and so on and the post-market process because you can, in fact, go back and continue the inspection process or evaluation potentially in lieu of clinical trials. Am I correct on that? From the manufacturer's side.

MS. TRAUTMAN: From the manufacturer's side, I wouldn't say it is necessarily in lieu of clinical trials because the quality system regulation is going to require quality system and then there is approval aspects that often dovetail. For example, if the manufacturer has a requirement from the Office of Device Evaluation to do

certain types of clinical trials, then what they need to do in their design control program is plan for that. So as part of the planing, they would obviously want to make sure that their clinical trial was a part of their overall design validation. That was the design validation I was telling you how they have to show the intended users.

DR. BOUGHMAN: It seems to me then that with regard to the total quality systems, we have several things in place. In the approval process, at least those that I have been involved in, we, in fact, do interface, interact with and have input with the manufacturer in the evaluation or in the data that we look at with regard to the device and its use outside the manufacturing setting. It is the post-market area that I am really asking my question about and I found it interesting today that a manufacturer came to us with a very different perspective of the independent studies done from potentially an academic scientist's point of view and not a user point of view and what I am really asking is the panel process and how we might be involved or what we might contribute to what I see is a gap here between pre-market evaluation which we are clearly very much involved in, some suggestions on immediate post-market evaluation but the out-years and there seems to be a gap here in what we

might do or even the FDA might do except request independent studies or look out for independent studies but we don't seem to be teaming up with that aspects in the out-years.

MS. TRAUTMAN: There is a couple of things that may help you. First of all, what I will call the post-market side of the quality system regulation is not something that is actually new. It has been around since 1978 but what it does, the new regulation does do is it does require the manufacturers to tie it into the quality system much stronger than it has in the past. In other words, they have always had requirements for complaint handling procedures.

The new regulation now requires that it not only be evaluated, investigated and so forth but it specifically says even though we have enforced it that you now have to take specific corrective or preventive actions when certain things are met. In the preamble of the new regulation which you all will have a copy of by this afternoon, we talk about user errors and user needs.

Just because complaint says that it is a user error, that does not eliminate the need for an investigation or possible preventive or corrective action. What the manufacturers may do is they may trend it over a certain

period of time and say no, this is not an isolated case once or twice. We are seeing this type of error on a more routine type of basis. Now we need to go back to our laboring. Now we need to go back to our design validation and see if there is something we can't do better.

In addition to the quality system regulation as you heard yesterday from Sharon, we do have the medical device reporting regulation. I think one of the comments by the panel members at the old committee here, I know, and I am not sure if Sharon is still here but I do know that there is a lot of training going on for the new MDR regulation and user facilities and doctors are on that list to be trained so the agency is trying to get that requirement out.

Where I think, this is my personal opinion, where I think a panel like this might be able to help in the post-market side is along the lines of what Mr. Cohen was saying. If there is some clear expectations as far as what you need as doctors to make some evaluations on certain specificities and so forth. If industry, FDA and experts like yourself can sit down and decide okay, this is the type of data we would like to see, this is the type of denominator aspects that we need to have to make these evaluations, and put that into either a guidance or into some sort of post-marketing

study, then I think that is the best way of pooling it all together so you have got the MDR regulations supplementing, you have got the quality system regulations supplementing and then you have got a task force, if you will, of experts looking but if that task force isn't focused on what they need to see up front, I don't think we will ever get there through any of the other systems.

DR. NIPPER: Before you leave, since you are there, if I could butt ahead of you, one of the things I appreciate about the information that you gave us and that I am learning to, I am trying to put into context and I believe I am doing it is that we are finally dealing with spec-ing out, if you will, the systems that are going to be manufactured and we are calling upon, we are re-echoing the age-old plea to the clinical community, if you will, the people who are represented around this table to try to figure out what we really want these systems to do.

Coming from a clinical laboratory background, a while ago some of us said how low do we really need to drive precision and how good do we want accuracy to be and how much are we willing to pay for it and have we done enough. I am not sure that we have done enough in self-monitoring, on the self-monitoring area but I think the challenge is out

there because I think we are hearing several people at this table and the audience say it is good enough. What we need to do is to train the user better.

How does your design approach of your getting in on the ground floor approach, how is that going to relate to the problem we have here with use errors? In other words, is that design, can you ask the manufacturers to design in that area as well?

MS. TRAUTMAN: Yes, we can. In fact, we can do a couple of things specifically to the errors and the user needs. Like I was starting to describe up front, we have a requirement for design input. The manufacturer is going to need to use multiple venues to receive input as to what they want to have as an output for their device. This panel or the PMA approval panels will dictate some of that, the agency will dictate some of that.

Their marketing people will help dictate some of that but the user community clearly also will dictate what those inputs and expectations are. So not only should that be all up front in the input, but also in the verification stages now they have to assure that okay, this is what I set out to produce. This is actually what I am producing.

And then the real key area for this panel is what

I referred to as design validation. That design validation is really the key now where the requirements under the regulation require either actual or simulated use condition of production lots to show that they meet the intended use and the user needs so this really is going to force more interaction; however we have to be careful because hindsight is always easier than foresight. When you talk about user errors, it is always easier to go back retrospectively and say all the device manufacturers should have known this.

But in reality, they may not have known that 10 years ago or five years ago when they sat down and were initially designing it so we do have to be careful that we do have a balanced perspective here, that the manufacturers need to make a good faith attempt to try to bring in those people that they are using or the people that will be using that device. The question earlier was if it is being marketed for both the clinical setting and home use, do they have to test both? And the answer is yes but we do want to be careful that every single way a user may misuse that device may not be thought of up front in the design.

For example, I mean, we often have clinical examples where doctors and nurses and lab technicians and so forth, clamp lines and do something and they just happen to

do it and don't realize the ramifications on a machine. We had apnea monitors and so forth that were tested in the home and they had vents in the back and all of a sudden a whole bunch of failures started happening because children started to put coins in the vents in the back.

I mean, there are always going to be certain things that no matter how much foresight a manufacturer has, that they will have to deal with on the post-market side.

DR. NIPPER: Let me ask you a follow-up question. Did you get to see that video tape from the mother of two diabetic children yesterday?

MS. TRAUTMAN: No, I'm sorry I didn't.

DR. NIPPER: That's okay. I think that might be worth 15 minutes of your time if you can get hold of the tape. One of the things she brought up were I tried to address in that wedge diagram about why do my monitors, the same monitor give me two different numbers five minutes apart, one okay, one not okay.

It brought to my mind to make a note about consumer expectations versus consumer needs. How does this design approach address the two different things? Because one may be, consumer needs may be a realistic need. Consumer expectation is Toyota performance but a Chevy

design. You know?

MS. TRAUTMAN: Right, I understand exactly what you mean. Labelling is dictated by two areas of the agency, in part by the approval process and in part by the design controls now under the new quality system regulation. Where in fact the labelling has to undergo the same type of design validation as the product itself. So the expectations are very important.

If the labelling clearly acknowledges that this, and again meaning to be in terms that the user can understand, that there is a 20 percent or a two standard deviation. They need to understand the ranges that these may occur. If the labelling is such that it says this is 98 percent accurate and if that is only showed by the manufacturer to occur on like the most ideal circumstances, we would say in the quality system that that is not accurate portrayal in the labelling for the design specs.

I am not suggesting at all that, I am just saying hypothetically because I have not reviewed the labelling for these devices but there is a truth in advertising or truth in labelling that what is in the label must be the actual performance specifications and so forth that are set forward in the design and then into the manufacturing.

So if this panel decides that that two standard deviation is an acceptable range, then it really is incumbent upon the labelling to make sure that the user understand that they can get a reading from that 160 to 240 and that is the precision of the piece of equipment.

DR. NIPPER: Okay. What I am getting at is suppose, I mean, this mother was ready to slam the device up against the wall because she was so angry that it was not reading correctly and what I am getting at is maybe correctly or maybe incorrectly, her perception of the way that device should perform is in her head. In other words, the label is in her head about what she expects. Suppose a company tries to design something that will meet this person's expectations but her expectations are not, exceed the performance that is required clinically. Suppose her kids were just fine, no mistakes were made, no adverse things happened, et cetera, and yet she is just disgruntled. How is the FDA going to look at that?

In other words, if they design to try to get a higher performance and they don't get it but yet they are still doing clinical okay, how does the FDA look at that? Are there different levels of consumer satisfaction or consumer client?

MS. TRAUTMAN: Clearly there is a different level of consumer satisfaction but the agency by law, by mandate, can only require the manufacturers to meet minimal requirements for safety of the product. So when I teach and talk about how other standards in New York and so forth are used, we can only in the GNP requirements and through other things require the manufacturers to do what is minimally or the baseline to assure that there is good quality products out there.

We as an agency from the compliance standpoint cannot mandate manufacturers to optimize for business reasons, again, that may be optimizing the processes. We can't really get into what we call quality management issues which is what you are starting to really come about and that is more of a pure customer satisfaction.

We have a line that we have to be careful that we don't cross because that is not really a regulator's job. That really is the manufacturer's interaction with their customers.

DR. NIPPER: So with the design we are still keyed into safe and effective and the other stuff is the whipped cream and cherry that the FDA is not concerned with.

MS. TRAUTMAN: Well, it is not that we are not

concerned about but there has to be different venues. The quality system regulation may not be the appropriate. They may be fully compliant with the quality system regulation. What we do have is in the Office of Surveillance and Biometrics, when we do have public health issues where we can show that consumer expectations clearly are here and the device's reliability even to the best of manufacturing is here, then we have task forces that are put together to do all kinds of different training, whether that be through newsletters, through bulletins, through recent venues of teleconferences now.

So it is not that the agency doesn't care, it is just what type of --

DR. NIPPER: It was an unfortunate choice of words, pardon me.

MS. TRAUTMAN: No, no, but I mean it is important to understand that there are training and educational efforts by the agency that would be different from the regulatory, mandatory things that we could take statutory laws and take them to court or do something like that.

DR. NIPPER: Thanks. Hang on just a second, there may be other questions for you.

DR. HABIG: I wanted to make a comment. It

sounded like you were leaning toward hoping that the quality system regulation will sort of fix the idea that manufacturers under the requirements of the new regs will be adequate in their assessment of customer needs. The regulation doesn't quantitate that at all. It simply says you have to have a process. You have to document the process. You have to validate you did what you said you were going to do.

If you have bad input, if you have inadequate input but it is well documented, the regulation doesn't say the input is, they can't judge whether the input was good or not good or adequate. It says you have to have a good system and you have to get customer input and once you make the decision of what the design is going to be, then you have to show you have met the design.

MS. TRAUTMAN: And that is where prospectively then the post-market aspects come in. Then, as you find out through post-marketing avenues with the complaints, MGRs or whatever, if you find that you may not have met those goals as well as you wanted to up front in design, the corrective and preventive action requirements now require you to take it back up, close the feedback loop and take those additional steps that you now learn are necessary.

DR. NIPPER: And see the problem that I am having that I am trying to sort out in my head in a very clumsy way I think, is how much of the stuff that we looked at yesterday that was quote, unquote, wrong with the system is stuff that deals with safety and effectiveness and how much of it deals with consumer dissatisfaction with A, the system, B, the device, C, the disease and all sorts of other stuff.

MS. TRAUTMAN: And getting the general feel for what that video had, I have a feeling the answer to your question is all of the above.

DR. NIPPER: Well, yes. Any other questions for Ms. Trautman.

DR. ROSENBLOOM: I don't have a question for her but since we are using that anecdotal experience, I think it is important to emphasize that not all systems are equal and those of us in practice have limited our patient's choices to a couple of meters that we trust. The one she was using was the one that I think everybody doesn't trust and I think that is an important thing to keep in mind. She was using a very unreliable meter and we have never found it to be reliable in all the testing we have done of it in the clinical setting.

DR. NIPPER: Thank you.

MS. TRAUTMAN: And the agency acknowledges that there are varying degrees of compliance to whatever regulation there is out there.

DR. NIPPER: Bob, thanks for your patience. I skipped over you.

DR. REJ: I don't have any questions for you. I have just a couple of observations and maybe some comments and what I learned and didn't learn this morning.

One of the presentations we saw that the error rate using the FDA reported adverse outcomes data is on the order of like 300 parts per billion in terms of adverse outcomes. Those adverse outcomes were really serious ones as I understand it. This is injury or death. This is the sort of outcomes that get associated with the airline industry and when I fly home to Albany tonight, I am going to have an expectation of getting Albany that is far above 300 parts per billion using data from the airlines.

I may not get there in time, I may end up in Syracuse. Since I am carrying my bag, I think my luggage will make it with me. But those are adverse outcomes that we are all more familiar with with the airline industry than the types of errors that are in the low parts per billion

error in terms of injury or death so I think that 300 parts per billion, even though it is terrific, is really high compared to the sort of standard comparison for these data and I am wondering if maybe some of the manufacturers and HEMA can put together perhaps sort of increase the information of the data base that the FDA and the panel are looking at by perhaps getting together a broader sense of the number of complaints as an idea of customer satisfaction for these devices.

Some of them may be just that they don't like the color of it, others that they have a real problem. The result that they read on the meter just doesn't meet what they feel their glucose is and that their action would be inconsistent with what the meter reading is and perhaps provide a hierarchy of how these complaints are dealt with and that might enrich the data base rather than the really the fatal or injury outcomes from them.

So that might be some data that are readily available without doing any really great study that might enrich the data that this panel of the FDA could look at.

This morning I heard clinical relevancy be brought up again. I fully agree with that. A colleague of mine likes to say that a difference to be a difference must make

a difference and I think that clinical relevancy is really the gold standard but on the other hand I see that there are a number of error grids that have been proposed so that is a little bit of a slippery scale so I can see why I, maybe it is because of my background coming from the laboratory side than the clinical side, you feel that this is the bottom line. You can't fudge that whereas clinical relevancy, somehow you have the impression of an individual physician treating a specific patient and you might be able to come up with a specific case where yes, for this patient, that small difference might, for a specific patient in a certain condition, a small difference can make a real big difference in a clinical, a wrong clinical decision will be made.

And I don't know how to balance these different error grids against the Nipper error grid that I saw this morning which basically said under the current state of the art 140 equals 260 and any other error above that is acceptable in some clinical criteria. That is a pretty big window so I would caution against trying to sweep some bad analytical data under the rug just on the fact that well, it is not going to make a difference clinically. I am not so sure that the current state of the art, 140 equals 260, is really the mark that we should be shooting for. Perhaps

physicians on the panel can educate me more.

And then just a comment on the CLIA limits that were bandied about. These are absolute, they are not 3SD limits. They are the limits that a laboratory gets decertified at and that is 10 percent. Go outside that more than once, a couple times a year, you are out of business so it is much more than 3SDs. This is a, the nine sigma value for a laboratory if they want to stay in business and that those limits of 10 percent are not for performance within the lab. That is a national standard. That is lab to lab to lab, instrument to instrument. That is a big, big pool and labs have to be well within 10 percent of accuracy on an individual basis.

DR. NIPPER: How far do you say within 10 percent? How far down do you go within 10 percent to try to get a feeling of adequacy in your own lab?

DR. REJ: There are a number of published models but I think if you are working at somewhere around, because some of it, there is a bias component that goes into that. You can sacrifice some of the, you can be somewhat more inaccurate if you are very, very precise and vice versa but I think the usual models are somewhere on the order of a half to a third of the CLIA criteria should be the criteria

within a laboratory before they are really afraid of getting into. However, I think many laboratories really don't know what their total, what their real inaccuracy is. I think we just sort of built it into a total error. They probably know that day to day with precision but total error is what they are really concerned about.

I think that is kind of the bottom line and I don't think that maybe the manufacturers are interested in teasing out all the different components because it is their business and they have all the data to do that but an individual user, they are just concerned about a total error budget, combined accuracy and precision and they know that they are going to be within that window and that meets clinical needs, 99-plus percent of the time, something like that. I think that is, certainly that is the way we look at it in our laboratory.

Maybe somebody from industry or HEMA might be able to comment on whether that data base would be useful, easily achievable and whether the other members of this panel might think that would be useful information.

DR. NIPPER: Our industry rep is chomping at the bit.

DR. HABIG: I wanted to talk specifically about

the fear and/or confidence you have about flying home to Syracuse or flying to Albany, right. Your bags will go to Syracuse if you check them.

The data that exists in the MDR data base does not tell us that a glucose meter system has ever caused the death or serious injury of a patient. MDR reports are required because there is an allegation that the system has been involved and I mean, there are anecdotal things that I have seen on specific cases where an MDR alleges, the MDR quotes that a patient die but alleges that a glucose monitoring system has contributed.

Other circumstances in some instances that are anecdotal but that I know of, the glucose meter, it is not possible to tell whether the glucose meter contributed and I just want to make sure that the panel doesn't go away with the understanding that from the FDA data base that anybody knows whether there is a cause of death or serious injury in particular of the deaths. I think I heard a number of 55 over the, since 1984 but they are, because of the reporting system it is not known that there is a causal effect and I think it is important not to go away or to have anybody go away with the idea that we know from that data base that a glucose meter system has ever caused.

We don't know that they have not. I just, the data is not sufficient to make that interpretation and on something else you said about the 20 percent, I guess I said this yesterday, devices cleared for home use for the self-monitoring of blood glucose have specific indications for use and they are not, for diagnostic testing. They are for self-monitoring of blood glucose and there are some assumptions in the indications for use which I hope I am saying that right, Sharon, which have an interpretation of serial testing of professional health care personnel interaction that is different from a one-time glucose value obtained on a patient in a hospital with a laboratory test.

DR. NIPPER: But self-monitoring blood glucose instruments are defined to include more than that according to the document that we are looking at today. I am going to quote from that definition. Portable blood glucose devices are intended for use in hospitals, at point of care, in physicians' offices and for use by lay persons. So this is a broad group.

DR. HABIG: All of that is true but they are intended in all of those places where they can be used for the self-monitoring of blood glucose. They are not labelled for diagnostic testing even when they are in the hospital.

It is following glucose --

DR. NIPPER: Even when they are used for that.

DR. HABIG: That is correct. I did not say they, that expectations of users were always the same as the indications for use.

DR. NIPPER: Right.

DR. REJ: But are they specifically labelled not for diagnostic use?

DR. HABIG: I don't think that is required in the labelling. I don't think that is any requirement by the FDA or something that manufacturers put in the labelling. They put in the labelling what the indications for use are. That is the requirement.

DR. NIPPER: Okay, let's make it brief and we will keep going.

DR. ROSENBLOOM: I just have a concern about the semantics of diagnostic use. When a patient calls me in the middle of the night, I am trying to make a diagnosis of ketoacidosis which is based on the blood sugar and the urinary ketones that they report to me or if the child is passed out, or has had a dizzy spell, I am trying to make a diagnosis of hypoglycemia so I think diagnostic use is a variable terminology here. Diagnosing diabetes is one

thing. Diagnosing the state of the patient is quite another.

DR. NIPPER: I understand.

MR. COOPER: I just want to endorse that.

DR. NIPPER: Thank you very much, Dr. Cooper. Did you have any comments or anything you would like to ask questions of the people who have presented this morning, Barbara?

DR. GOLDSMITH: Not so much questions as one comment referring to quality control. Mr. Kimmelman did address quality control and I understand it is a very difficult issue to deal with and I was struck yesterday by some of the data we saw with the complaints, the trends that about one percent of the problems reported were related to QC and I don't know if that was because it was problems with QC itself or people don't use it.

But we have heard from the users that there are problems in using the meters. Dr. Nipper I thought very well described the widespread that you see and the 20 percent error leads to that very wide, acceptable error, leaves that very wide spread so I think it is important to be able to try and figure out where the problem is and QC I think is a way of doing that whether it be the user, the

device, or the spread and I learned also recently, yesterday, that there are a variety of combinations out there with people using different strips with different devices so I think it would be important for the manufacturers to provide a way that the instrument can't be used, the device can't be used without also using quality control or having the user run QC.

MR. COOPER: I have a question for Mr. Kaye and I also wonder if somebody from industry could also respond although I would not select anybody, just anybody who wants to answer. Mr. Kaye, I got a lot from your talk about human factors. One of the issues that I guess we are all dealing with is the concept of does one size fit all and we are looking at that in different perspectives. I wonder from the human factors perspective, in your opinion, is it possible to develop a set of guides for human factors that would encompass all the potential uses for these meters like old people, young people, adolescents in the hospital or do you just have a gut feeling that it would take different sets of human factor guides for those different users in different situations?

MR. KAYE: I think that may very well need to be done. That would be difficult to do because of all the

variability involved. General guidelines, of course, are helpful and education is helpful. As for specific guidelines, that would take a lot of analysis and a lot of data and a lot of clarification of the situation that I don't think we have at this point. I think it is a very good idea. It is a very nice to have. Whether or not it is practical in the near term, I am not sure.

MR. COOPER: Is there anybody from industry who would like to comment on that? Does one, is it conceivable that one size fits all for human factors or is it reasonable to have separate kinds?

MR. KIMMELMAN: I tried to touch on that a little bit in my talk when I spoke to you about parametric standards. I think it is very difficult if not impossible for a panel like you to say that you must have either this design characteristic or this design specification and that particular specification would suit all the potential users but it is certainly within your ability to let us know what issues are important in terms of visibility, in terms of size, in terms of manual dexterity to tell us what issues have to be addressed and to put the manufacturer to the test of applying what Kim is talking about in the design input to find out what the specifications need to be for particular

patient populations or particular users.

And then look at the information that the manufacturer puts together as they try to apply their product to a particular population so in that regard, to me that is the real value of the parametric standard. Tell us what is important to you as a clinician from what your experience has been in the use of these kinds of systems and then put it, put the manufacturer to the test of gathering the information with respect to that issue with respect to that particular population and then see how well the manufacturer has designed to those kinds of input requirements.

MR. COOPER: Thank you, that is very useful.

DR. NIPPER: Dr. Zawadzki, do you have comments or questions?

DR. ZAWADZKI: I was just thinking about a broad comment that I have been thinking about but since we are going to have further discussion this afternoon, I guess I will defer that.

DR. NIPPER: Thank you. Dr. Kurt?

DR. KURT: I have several areas that I think could be focused on but I think it might be better to wait for the beginning of the session this afternoon.

DR. NIPPER: Okay, Dr. Rosenbloom?

DR. ROSENBLOOM: I think I will defer also since you are running about 15 minutes late.

DR. NIPPER: Okay. I am going to want to run about three or four more minute later because I would like to ask the Executive Secretary to put up some questions so that we can remind ourselves of what our goals are this afternoon. The first goal that we have already begun to address is how are patients being managed. The second goal is that we would like to address in our comments is to determine what goals are appropriate for different groups of patients and different treatment regimens which Dr. Cooper just eloquently discussed.

I am concerned about goal number three, what device performance is needed. I tend to regress to my analytical chemistry background in that area. We may or may not want to spend more time on goal number four which is, has evaded us as far as the transparency goes but it is to discuss current technology and its performance capabilities and limitations and then the fifth goal is to identify areas in which the agency, professional groups, patients and manufacturers can work together to achieve the various goals of glucose monitoring.

I think we are touching most of these goals reasonably well. This afternoon we are going to have three more presentations. I apologize, we are going to have two more presentations. Ms. Hensen presented yesterday. And then we will have open committee discussion about these goals and we will try to address them one at a time, go around and get as many comments as we can at that point and then try to get Bob Rej on a plane to Albany.

Since we are starting lunch late, I would like to reconvene, my watch says 12:24. I would like to reconvene at 1:30. I am on chairman's time here.

(Whereupon, the meeting was recessed at 12:20 p.m. for lunch.)

A F T E R N O O N   S E S S I O N

DR. NIPPER: So we are back in session. We have a quorum. Into open public session. I won't tell you to disclose your financial involvement. Public attendees who contacted the Executive Secretary prior to the meeting will address the panel and present information relevant to the agenda. Speakers are asked to state whether or not they have any financial involvement with manufacturers of any products being discussed or with their competitors.

That being said, we are privileged to hear from Dr. Frederick Kiechle from ASCP. ASCP says it is in Washington and I am not sure where Dr. Kiechle is from but he will tell us.

**Agenda Item: Dr. Frederick Kiechle, ASCP**

DR. KIECHLE: Okay, thank you very much. It is Kiechle, rhymes with weekly.

Good afternoon, Dr. Nipper and members of the panel. My name is Frederick L. Kiechle. I am chairman of clinical pathology at William Beaumont Hospital in Royal, Michigan, and I am here today speaking on behalf of the American Society of Clinical Pathologists where I serve on the Continuing Education Council on Clinical Chemistry. I have no financial interest in any self-monitoring blood

glucose system or systems although I have been involved in the evaluation of a variety of these devices at my hospital over the years.

ASCP for background information is a non-profit medical specialty society organized for educational and scientific purposes, has over 75,000 members, including board-certified pathologists, other physicians, clinical scientists and certified technologists and technicians. We recognize the society as the principal source of continuing education in pathology and as the leading organization for the certification of laboratory personnel.

Overall, we are pleased with the general quality of the Food and Drug Administration's comprehensive document on review criteria for assessment for portable blood glucose monitoring in vitro diagnostic devices using glucose oxidase, dehydrogenase or hexokinase methodology. However, there are a few areas that need revision based on current data and many other comments I will make have been addressed, some have been addressed in part by other speakers.

Looking over current data, by our review, we have got no references listed beyond 1994 despite literature to the contrary which has been reviewed in depth by other speakers. Specifically, there is no reference to the

approved 1994 guidelines from NCCLS, the C-30-A. These guidelines discuss the appropriate uses of bedside glucose testing in a hospital setting and the administration, the institutional authorization process, the method for verification of instrumentation quality assurance procedures and may be used for background purposes for the document or guidance.

The American Diabetes Association consensus guidelines quoted in the document were from 1986 and the ADA as we heard published a more recent consensus guidelines in 1994 and, according to these guidelines, the analytical goal, what that is exactly we are not sure, for future self-monitoring blood glucose devices should be plus or minus five percent. Of course, the question is five percent of what.

The assessment of clinically significant errors by methods such as the error grid analysis needs to be refined. The document notes that the Cox Clarke error grid may be used to estimate clinical significance of bias results between methods but does not note the source of this information nor its need for refinement like in the case of hypoglycemia. There is also no reference to the FDA's 1996 data reviewing greater than 400 medical device reports on

blood glucose monitor views in hospitals. This was reviewed in a Health Devices article in 1996.

This information probably should be added into the section under human factors studies and the problems that were listed as the top five difficulties, with meter use in a hospital setting included the incorrect quality control or proficiency testing procedure, the improper technique, incorrect match between monitor calibration and test strip calibration, inadequate cleaning, and inappropriate blood glucose monitoring lab comparison and their greatest problem is probably not using a fasting specimen.

The article in Health Devices which included this FDA data does include recommendations for correcting many of these human factor problems. There are other issues we would like to bring to your attention as well.

On page three, the document should expand upon the description of pre-analytical, analytical and post-analytical factors. On page five, the device description of glucose dehydrogenase method used by the hemocue which is a whole blood method with red cells lysed by saponin should be distinguished from another glucose dehydrogenase method used by Barry Mannheim which uses whole blood method but does not lyse red cells.

In the correlation study section, it is important to separate those point of care testing glucose methods that lyse red cells and therefore measure true whole blood glucose from those that do not lyse red cells and measure therefore probably plasma glucose. It is highly inappropriate to use whole blood YSI for hexokinase methods in a central lab to compare a point of care glucose method that does not lyse red cells.

Overall the document would benefit from a discussion of point of care methods using glucose dehydrogenase and whether advice on methodology lyses red cells or does not. In the section on labelling, the document should expand upon the list of pre-analytical, analytical, and post-analytical factors and specifically one item is the issue of hypertension. Finger stick specimens should never be used for glucose or any other analyte if the systolic blood pressure is less than 80 millimeters of mercury because the blood is centrally located and very little is found in the finger in which you obtain this interstitial juice.

Newer methods provide for the expansion of the high and low glucose values to about 40 to 400 milligrams per deciliter. Health care professionals should evaluate

their technique and their patient's technique three times a year to test at term periodic intervals under item six is not specific and expiration date for blood glucose strips storage should be explicitly listed. Glucose sensors using glucose oxidase with a pterocyanide ion underestimate glucose values with high oxygen concentration. That is high PO<sub>2</sub> values and the glucose error reached a plateau of about a minus 21 milligrams per deciliter at PO<sub>2</sub> values greater than or equal to 150 millimeters of mercury in this study.

This effective oxygen administration should be noted under item 13. Dopamine will inhibit glucose oxidase and should be so noted. Arterial whole blood determined by glucose oxidase strip in one study was significantly higher compared to arterial serum glucose and in this study, published by Mazer et al., 31 of 50 patients would have received an incorrect insulin dose if arterial whole blood glucose values were used.

Arterial blood is appropriate for glucose dehydrogenase and hexokinase methods.

The section on limitations mentions that variability of more than 20 percent is an acceptable range. The goal of all self-monitoring systems should be a variability range of 10 percent; however, a more recent ADA

consensus conference has suggested plus or minus five percent of something so there is some confusion and we have heard that described in detail.

DR. ROSENBLOOM: Is that more than 20 percent or no more than 20 percent?

DR. KIECHLE: It should be no more than 20 percent. That is an error, sorry.

And then the future. In the future, non-invasive methods for blood glucose measurement will become available. And there are two major techniques used today, radiation technology and fluid extraction technology. Six primary technologies are under investigation at this time, near infrared light spectroscopy, the far infrared radiation spectroscopy and radio wave impedance, optical rotation of polarized light and fluid extraction from skin and interstitial fluid harvesting. The document should address some of these future technologies.

I have a few comments based on recent literature and my own experience about current patient management goals, treatment regimes and advice performance.

First, should hospitalized type two diabetic patients be treated with a sliding scale insulin dose given four times a day which require four finger stick glucoses or

other glucose measurements prior to giving the insulin dose? Many hospital laboratories find it difficult to adjust the phlebotomy schedule around food delivery. At my institution, failure to provide a glucose result to a 21-bed diabetic unit 26 percent of the time resulted in additional nursing costs, sometimes called external failure costs of more than \$45,000.

A recent publication in the Archives of Internal Medicine by Quale, et al., from Johns Hopkins, questioned the value of sliding scale insulin with multiple glucose measurements. They found the rate of hypoglycemia and hyperglycemia on patients with sliding scale insulin to be higher than type two diabetics treated without a pharmacological regime and they concluded that sliding scale insulin with or without a standing dose of intermediate acting insulin was of no benefit in hospitalized type two diabetics.

The impact of this study may result in a great reduction of capillary blood glucoses in a hospital setting. Outcome studies need to be designed to evaluate the value of sliding scale insulin in hospitalized type one and type two diabetic patients.

And one last thought, regarding neonates, what we

really need is a glucose meter to be manufactured with a coefficient variation of less than five percent in the range of 0 to 100 milligrams per deciliter glucose to be used in the newborn nursery and/or the neonatal intensive care unit. Neonates have at least one serum glucose that is less than 40 milligrams per deciliter in the first two days of life and, according to several authors who have attempted to use a variety of reagent strip methodologies or the hemocue methodology in the NICU, the neonatal intensive care unit, they have found an acceptable coefficient of variation of less than five percent in the 40 milligram per deciliter range. There is a great clinical need for a device that will perform well with high hematocrits in the range of 0 to 100 milligrams per deciliter of glucose.

And, in conclusion, thank you for this opportunity to comment on self-monitoring blood glucose systems and I would be pleased to answer any questions you may have. Thank you.

DR. NIPPER: You are welcome. We have, according to the traffic light on the podium, a little time left for questions if the panel members have any.

DR. ROSENBLOOM: I am glad you brought up the issue of the sliding scale. I despise the term. That goes

back to the days when we were chasing urine values and putting people into hypoglycemia, sometimes fatally but the issue remains the same with the concept of the sliding scale. No one has yet figured out a delivery system that makes insulin work backwards and to treat an elevated blood sugar is shutting the barn door after the horse has been let out. What it does not constitute a well-thought-out management program. Supplemental insulin for dangerous hyperglycemia is rational. Day to day management, treating blood glucoses as you measure them, is not rational because you should be keeping the blood glucoses from going up or going down inappropriately by your decisions earlier.

So I think your comments about sliding scale are very appropriate and I would be delighted if particularly in at risk, highly at-risk older patients for hypoglycemic brain damage or strokes, if these observations led to a reduction in the use of the so-called sliding scale in hospitals, a very dangerous practice, and I would be interested in the internist's comments about that.

DR. NIPPER: Dr. Zawadzki, you had your hand raised as well.

DR. ZAWADZKI: Actually, I had my hand raised to ask why three interactions with a health professional was

selected as a goal.

DR. KIECHLE: That is a very good question. I believe that the more important message is that a number be chosen rather than using the number periodic and three is certainly not a gold standard.

MR. COOPER: I certainly agree that the sliding scale is awkward and most of the time not appropriate but the problem that we on the panel and the FDA is going to face, however, it is going to be a long time before we get rid of that. And so the issue is given that it takes a long time for behaviors to change and for adequate studies to build the evidence that is persuasive, what do we do in the meantime even though I agree with what you said.

DR. NIPPER: Dr. Kurt?

DR. KURT: I certainly agree with Dr. Rosenbloom concerning the chasing of the blood sugar with the sliding scale but the concept of changing it gradually has to do with educating the health profession to be anticipatory. I agree with the point that you have expressed and pointed out many important items that the FDA really has to look into from the standpoint of a futuristic approaches.

DR. NIPPER: I can hear in my mind the great educator at the University of Maryland, Dr. Ted Woodward,

responding to a junior medical student about treating a number and his great outrage at that. He said treat the patient, not the number. I think that that is a good anchor for your comments, Dr. Kiechle. While you are here, on the podium, I wonder if Dr. Gutman could help us with the issue of hospital use of self-monitoring blood glucose devices. Are we working on that or are we working on that on only self-monitoring blood glucose devices used in the home?

DR. GUTMAN: Well, I think actually Mr. Plume(?) brought up the interesting issue that this is a complex document and you might look at breaking it down into several components when this, the underlying drive for this particular conference, this particular panel meeting, is to look at the home use. I don't know that you exploded from looking at a broader view so I don't now that one intelligent thing might be as we move forward for us to perhaps have different documents, one for home use and one for professional use and the two will inevitably get mixed up.

Sharon Lappalainen, your exec. sec., pointed out to me earlier that when there was some discussion I might point out to this group, it is a little late but I will point it out anyway, that as products come through, they are

very prime driven and that we start with an intended use. An intended use for these products, in fact, are all the same. They are all to measure glucose and you can link them to a classification scheme as a class three product as was said yesterday. And then what refines them is their indications for use and some of them are frankly keyed in to be used by the lay user at home and some of them might be specifically to be used at alternative sites and unfortunately some of them, it may not be as clear and there is, because of the reasons we talked yesterday, this problem with the overlap with CLIA so we are here to learn and listen and the major focus is looking at lay users but if the other gets mixed in, we want to talk about what we can do to help make that better or clearer.

DR. NIPPER: While I have the floor, I would like to ask Dr. Kiechle if it has been your experience that the hospital use that you refer to, if the patients themselves are doing their own glucoses or whether the staff, hospital staff is doing the glucoses on the meters for the patients or if it is some mix thereof or how does that work in your place?

DR. KIECHLE: That is a good question. I will try to describe how it works at our place. We have what we call

selected nursing units that have the nurses, the RNs themselves for the most part and in only rare cases is it an LPN. They are trained to use the reflectance meter technology and we call it selected nursing stations. We have a point of care testing committee that meets on a regular basis to discuss anything that looks or smells like a laboratory test that is going to be used out on the floor by non-laboratorians and the committee's membership is variable depending upon the topics that are being discussed but in case of blood glucose monitoring devices, the committee is interested in understanding why the central lab can't provide the turn around time that is required for patient care in that situation.

And then, secondly, we are real interested in how patient outcome might be benefitted by having this program on a nursing unit. The most persuasive argument is that there is a large number of diabetic patients located on this floor. Ten percent of the population in the United States is diabetic so it if it is ten or greater percent of our hospitalized population has diabetes and they are located everywhere throughout the hospital.

We have excluded glucose oxidase technology from the ICU and the ER for the reasons that I alluded to. There

are two potential potential problems, the blood pressure problems, and we train these nurses. I have two full time FTEs, medical technologists who are responsible for non-laboratory people doing lab tests. We do all the initial training, teaching, competency evaluation for all these people. Does that answer the question?

DR. NIPPER: All except do any patients do their own testing.

DR. KIECHLE: Okay, that is a great question. In C-30-A, the NCCLS document on bedside glucose testing, it describes their method of handling that particular problem. We instituted that at William Beaumont hospital and the goal, what happens is if the patient arrives and is judged by his or her physician to be well enough to warrant the bedside glucose testing using their home device, they are free to bring that to the hospital and do their own monitoring. The laboratory is out of the loop. It is between the nurses, the patient and the physician, the health care team providing care for that patient.

DR. NIPPER: So basically you are dealing with this as a point of care testing issue with a few exceptions.

DR. KIECHLE: That is correct.

DR. NIPPER: Okay. Dr. Zawadzki?

DR. ZAWADZKI: I just had a quick question about that. When one of your patients uses his or her own meter, do you compare the value with a simultaneous laboratory measurement?

DR. KIECHLE: We certainly can do that if it is requested. We have a program in place for the nurses who are doing the testing to do one meter comparison per day so they will select a patient who is really have a venous glucose done for another reason.

DR. NIPPER: Dr. Rosenbloom, you had your hand up earlier.

DR. ROSENBLOOM: Yes, I think my question was answered. This is basically what we do at our hospital. It is a highly controlled system and they have special equipment. And everybody who is authorized to do it is well trained and has got a very intensive QC.

DR. REJ: Do those patient performed test results get entered in the patient record or on the chart?

DR. KIECHLE: I think that varies depend on what unit you are on. They are certainly on the chart. They might be in the nurse's notes, they might be located on a flow chart.

DR. REJ: Is there any guidance in the NCCLS

document regarding that?

DR. KIECHLE: There is not that I am aware of.

DR. NIPPER: Are there any other questions for Dr. Kiechle? Any other comments I should say. Thank you very much.

DR. KIECHLE: Thank you.

DR. NIPPER: Our next presenter is Jim Nichols from the American Association for Clinical Chemistry.

**Agenda Item: Jim Nichols, American Association for Clinical Chemistry**

DR. NICHOLS: Thank you for the opportunity to address and appear before the Clinical Chemistry and Toxicology Devices Panel. My name is James Nichols. I am associate director of clinical chemistry at Johns Hopkins Hospital and assistant chief of the Johns Hopkins patient testing program. I am here on behalf of the American Association for Clinical Chemistry. Today I will discuss some of the most frequent causes for inaccurate readings of glucose meters both in the home and in the clinical settings and offer some practical options for addressing those problems.

The advent of glucose meters has allowed diabetics to better control blood sugar, thereby delaying the long

term complications of their disease. Use of self-monitoring blood glucose systems in the home environment has provided a better understanding and prevention of individual factors affecting blood glucose but most important it has allowed patients to become active in their own treatment, educate themselves about their disease and to take charge of health through preventive measures.

But for all their advantages to the home user, glucose meters in the health care environment have opened the door to a world of technical and operational issues that still plague these devices today. Health care institutions are very different than the home environment. Home patients are generally well. They are ambulant, have normal hematocrits and can easily use capillary samples to trend their glucose levels.

In the health care institution, a patient may enter the system through the emergency room, have surgery in an operating room, spend time in an intensive care unit followed by a general medical unit and then have follow-up in an outpatient clinic or a physician's office but the patient will typically have glucose results from different glucose meters on several nursing units operated by multiple staff with differing educational levels. The patients may

have arterial, venous, or capillary specimens drawn depending upon their care statements and their point of care glucoses will be interspersed with laboratory values.

However, clinicians will treat the patient with standard insulin regimens that were created against laboratory values. If a glucose meter is biased with respect to the laboratory, then inappropriate therapy may be initiated. Accuracy and correlation to a well-characterized comparative method is a primary concern in health care use of glucose meters. Consensus panel statements recommend meter correlation to within plus or minus 15 percent of the central laboratory from the diabetes care 1987 consensus panel.

A study performed at Johns Hopkins in 1993 examined four second generation no white glucose systems using a limited number of highly skilled laboratory technologists. That study found that laboratory agreement consensus panel standards within plus or minus 15 percent varied from only 58 percent to 96 percent on samples from our typical inpatient population. These were a mixture of arterial, venous, and capillary samples.

The sources of low agreement were hematocrit bias, use of arterial blood samples and calibration differences

among the different meters. All the meters except one were noted to have a significant hematocrit bias that varied with the level of glucose. Calibrations generally assume a normal hematocrit range of 40 to 45 percent hematocrit and do not take into account the anemia of acute and chronic illness that is noted on hospitalized inpatients.

As a point of comparison, our average inpatient hematocrit average about 32 percent hematocrit. Devices without hematocrit bias lysed red blood cells and determine a whole blood glucose. Test strips, however, demonstrate varying degrees of cell lysis and plasma contact with the chromogenic reagents. The type of sample can further affect results because of oxygenation effects, predominantly with glucose oxidase strips and sampling artifacts such as normal arterial venous differences or inappropriate fleshing of lines.

While some meters are whole blood calibrated, others are plasma calibrated and still others mathematically correct a whole blood result to simulate plasma. The net effect of these differences leads to a variable agreement with laboratory results and difficulties in clinical interpretation. Clinicians typically do not take the time in an emergency room or an ICU to determine the patient's

hematocrit in order to offset the expected point of care glucose with the laboratory result before they institute treatment, nor do the operators of these devices routinely check the patient's hematocrit prior to analysis to insure that patients are within tolerance limits for their particular meter.

Accuracy remains an issue today. In another study we conducted last month, five glucose meters demonstrated laboratory agreement of 86 to 98 percent. While this is better than our previous study, this data indicates that improvements are still needed with respect to reducing hematocrit effects and standardizing glucose meter calibration to match the laboratory plasma serum standard.

Precision is another issue separating home and health care use. In the home environment, patients use a single device on themselves. This yields tighter values that in a large hospital which may have more than 100 meters and over 1,000 operators.

The consensus conference recommends precision of less than five percent CV, coefficient of variation. In our original study, laboratory precision of two to seven percent CV obtained with a small number of operators under well controlled conditions jumped to 1 to 20 percent CV when

tested on nursing units with multiple operators. Even our meters in routine hospital practice demonstrate overall CVs of two to four percent in the laboratory and four to six percent on the nursing units.

Clearly, glucose meters are not entirely free of operator effects and variability increases with the number of operators. Initial consideration of device approval and labelling specifications and package inserts needs to include data from home users or health care professionals or both, depending upon the intended user of the product.

In addition to the technical limitations of glucose meters, there are also operational differences that cause difficulties. Advances in data management have made these devices more adaptable to institutional settings by helping them to meet the regulatory requirements. Today's software can track quality control, operator and meter statistics. Some meters can even maintain patient records.

Unfortunately, much of the software is unfriendly, requiring input of up to 30 numbers for lot, control, patient and operator identification for each test performed which operators frequently will try to bypass in order to save time.

Even with bar code scanners to get the data into

the meters, the statistical computations, compilation and review of control and patient reports still require significant amounts of labor to manage. Our institution has three dedicated FTEs to manage point of care testing. It takes one person three days to just walk around and collect the data from the 130 meters that we have in clinical use and another five days to compile those reports.

The staff also conducts technical checks on new meters on arrival, validates test strip and control lots, inspects nursing units, and follows up for regulatory compliance and monitoring of our internal QA monitors.

Manufacturers should continue to work with health care institutions to streamline their data management, automate report generation for regulatory compliance and try to minimize labor input.

Initial device training and maintenance of operator competency records are major time consuming activities. Initial conversion to our current glucose device in 1994 involved forming a QA program, writing educational materials and developing standardized training checklists based on written procedures. Training was estimated to cost over \$35,000 with the investment of 500 additional hours of administrative time organizing the

program and one hour of hands-on time training for each of 1,800 operators.

Despite this time investment, there was still the need to follow up inconsistencies and procedural issues over the last three years by our quality assurance staff. Operators were noticed to be allowing blood to clot prior to analysis because they were transporting the specimens to a utility closet on the nursing unit rather than performing the analysis at the patient's bedside. This resulted not only in inappropriate glucose levels but damage to several of the meters.

Other operational problems stem from the manner in which the glucose meters are used. Home nurses typically carry glucose meters in their cars to deliver care in a patient's home. Few nurses routinely remove these meters when they park their cars. The meters, test strips and controls are thus exposed to extremes of heat, cold and humidity that can compromise results. Operators are also unlikely to wait the recommended time to bring the test strips and controls to room temperature prior to testing when emergency situations arise.

Critical action values are still another problem. Institutions generally set panic values in the high and low

ranges of 400 to 500 milligrams per deciliter and 30 to 50 milligrams per deciliter with recommendations for laboratory confirmation outside of these levels. Yet, currently marketed devices are capable of reading far beyond these limits with variable agreement to the laboratory.

Few clinicians are actually going to wait for a laboratory result prior to starting treatment. I have actually seen patients sent into hypoglycemia because insulin dosage were given when using levels of 500 to 600 milligrams per deciliter, levels previously determined to be inaccurate on this particular device.

Treatment was started because the meter gave a quantitative result rather than a high or panic error message, reminding the operator to question this result. The data management software of glucose meters needs to be customizable so that quantitative results are not given out in ranges outside of laboratory-determined agreement.

Recent advances in the lock-out features of data management, however, have made the meters more compliant with regulatory requirements and significantly impacted the quality of the results. These new devices allow health care institutions to lock out patient test performance if the devices do not pass quality checks or quality control has

not been performed within a defined time frame.

This feature assists health care professionals insuring that patients are not treated on glucose results when the meter is malfunctioning. Oversight of meter use in a health care institution is necessary to guarantee that the device is capable of giving the right answer, being operated correctly and is suitable for its clinical application yet regulation should not be so stringent as to make compliance difficult.

Data management upgrades that allow institutions some level of meter customization will improve regulatory compliance through automatic and transparent documentation. Point of care testing also needs to be integrated into critical pathways to insure utilization on appropriate patient populations and to improve clinical outcomes.

Manufacturers by working with physician's office labs, home health care nurses and hospital staff can best determine the necessary improvements needed to make glucose meters more accurate, simpler and adaptable to health care use. Future FDA review of glucose meter applications must take these technical and operational issues into consideration.

I would like to thank you on behalf of the AACC

and myself for the opportunity to present this data to the committee today and I look forward to answering any of your questions.

DR. NIPPER: Thank you, Dr. Nichols. Does the panel have any questions at this time for the presenter? I have one. Is it your view that home blood glucose monitoring devices as used in your institution are adequate as built to meet the quality specs for patient care, given the extra effort that you and almost all of our other institutions do to make sure that the operators are trained and so forth. In other words, are they accurate and precise enough for their intended use?

DR. NICHOLS: I think as we showed from our data, it depends on the device that you are particularly talking about. Each device tends to vary with agreement to the laboratory. As we showed in our previous study, it could be only 50 percent of the time that you are within that two SD limit as you had mentioned so you need to figure out which device actually fits and matches your laboratory the best, given that a lot of the data management is not, I don't know any of the data management that has a flawless, seamless, transparent documentation. There is initial output of labor and ongoing output of labor involved in keeping these up.

The bottom line comes out to whether it is beneficial to the patient.

I think that yes, there are glucose values out there that have significantly impacted patient care and have assisted the clinician in the emergent treatment of patients. So I think used judiciously, they are very beneficial.

DR. NIPPER: What I am getting at is assuming it is a perfect world and you could write specs for an appropriate point of care glucose tester. Would you, are there particular points about the current, and I am not talking about specific instances. I know that we all have to pick and choose the instruments that are appropriate for our own institution but in general would you tighten the performance specs or in general are they adequate?

DR. NICHOLS: I would definitely tighten the performance specs because even last month we were getting agreement of only about 85 to 90 percent. Some of the meters were up close to 100 percent but they are not near the two SD limits that you would expect if the consensus conference standards were plus or minus 15 percent. That is on the technical side.

On the operational side, the data management is

severely inadequate for most health care use, even given the ability to track patients to track quality control, they don't track it like a laboratory information system. They are not able to do relational comparisons, lot comparisons, control comparisons between operators, between lots of strips and controls, between institutions or nursing units so until the data management reaches that level, you continue to have to put in manual input into these to make the clinical judgments of whether the device is operating properly or not.

DR. NIPPER: So in essence it is like going back to the days when you had a Coleman junior and recorded things in your lab manual. That is basically what we are talking about on the wards and you could put the Coleman junior in your pocket and walk around with the reagents and do it and write it down again.

DR. NICHOLS: I don't know if it is quite that far back.

DR. NIPPER: That is going a long way back.

DR. NICHOLS: It is in an intermediary stage to where it is not advanced to laboratory standards and what the laboratory information systems are able to put out today and a lot of the meters are not able to talk with laboratory

information systems. They are working I know most of the developers and manufacturers are developing interfaces but the data bases to do these statistical comparisons that are necessary for clinical judgments are not there yet.

DR. REJ: Do you see that as a requirement or as a feature of convenience?

DR. NICHOLS: I think it should be part of the requirement of going into an institution used for health care use because all health care institutions have to meet regulatory compliance. JCHO or CAP, whoever, or state, whoever their certifying agency is so in one fashion or another they either have to manually calculate the statistics and manually document operator competencies on an ongoing basis or they have the computer do it automatically from quality control records.

**Agenda Item: Open Committee Discussion**

DR. NIPPER: Any other comments? Thank you very much. At this point I think we have reached the end of the list here unless there is somebody else. So I think we are ready to start with our goal. The way that I would like to do this is to take the five goals and go for one through five and go around the room and take any comments that we have about those goals or whatever else the mood strikes you

to talk about at the time and then at the end when we finish number five, I would like to go around one more time and anybody who wants to get anything off their chest at that point can do so. I would like to invite during that time we will open it up for the FDA staff to comment or ask questions if there are any last comments, assuming that they are not extremely long winded from the people in the audience that have presented, I think we can do that as well.

So I don't want to be grossly unfair. We started at either end yesterday and started off to the right of me yesterday so Bob, I will put you on the hot seat today. Dr. Rej.

DR. REJ: You are going to take each goal one at a time?

DR. NIPPER: We are going to take them one at a time but I am not going to be too much of an ogre if you stray. These are general questions.

DR. REJ: I see one and two being awfully interrelated and hard to really limit or exclude two in addressing one. And I think at least it became clear to me that it is very difficult, let me first see the two large groups of patients. There are groupers and there are people

who are dividers. I am a bit of a divider and I see there are really two groups of individuals being served. One is the actual home use part of the home use device. Then there is the professional use of the, quote, home use, device.

I never really thought about it in this way before. I think that the requirements for these, these uses of the same physician instrument are different enough that I think it would be very difficult to come with a single document for both of these uses. I see these uses as being disparate enough that I would find it hard to physically do that. Maybe it is possible, someone with a lot more talent than I have might be able to do it but I would say that these are the two main groups, at least looking at it from what the FDA's perspective is and I would tend to recommend having two different guidance documents, one for a device, actually believing in the home use part of the home use definition and the other is professional use of an identical device or the same device or a very similar device.

This same panel saw a presentation by a sponsor of a specific device, not for glucose but a product aimed for a diabetic patients and basically was the same device for both for home use and for professional use and I would see these are being the two groups that are being served, the groups

of patients that are being served and treated and results that are obtained by these devices are acted upon by them and their physicians and at first blush I would recommend that there be two different requirement documents, one for a home use device and home use in one for, quote, home use device in other professional settings.

DR. BOUGHMAN: I would, in fact, concur with Dr. Rej's summary and I think the comparison and contrast of yesterday morning with the context that we have been looking at for the rest of the time is a useful one because at one point we were asked about the equivalents, the substantial equivalents and, in fact, we were talking about exactly the same machine but in fact, the answer to the question, are they substantially equivalent was not a pure yes. And I think that really crystallizes what we are looking at here and that was one device with certain kinds of complications certainly and not simple and straightforward but here we are talking about a whole variety of devices and much more complexity in the process and in the big picture.

So that in fact some of this might be handled in the labelling versus in calibration or in part of the management of the systems but I think that it might be very useful for the FDA to examine the possibility of splitting

these documents.

That would also, I think, address some of the industry comments about wanting some degree of specificity in guidance but at the same time that the panel or the FDA is not overly prescriptive and if, in fact, the manufacturers could tell one from the other, and make their guidelines accordingly and do their studies accordingly it would clarify the issue.

DR. NIPPER: Thank you. From the standpoint of a practicing physician, Dr. Harrington Fall, what is your perspective on how patients are currently being managed and what goals for these different groups of patients and different treatment regimens do we have?

DR. HARRINGTON FALLS: I can see that we are looking at monitoring motivated patients but we are also, we have a device available that can be used as a screening technique that some people might try to use to determine if they need to see a health care provider and so that is where the management and clinical practice is really going to be.

DR. NIPPER: Do you see instances in your practice of these devices being used in hospitals?

DR. HARRINGTON FALLS: Oh, yes. The convenience exactly as one of our speakers had said of you need it at a

certain time and it basically ends up being a rush hour log jam in the laboratory so that you cannot get the values that you want in a timely manner makes it very helpful to have on the unit and I have OB patient as well as diabetic patients that are using these monitors either short term or long term.

DR. NIPPER: Do they use them themselves or does a professional, is that a professionally used product for those patients?

DR. HARRINGTON FALLS: They are using them themselves and being instructed by a health care team which educates them.

DR. NIPPER: Ms. Rosenthal?

MS. ROSENTHAL: First of all, I have been sitting here very quietly this afternoon but I think I am going to make up for that now. I count four sets of standards and I suspect that that might be able to be three but I think neonatal is one. I think juveniles below the age of 12 may be one although that could be coupled with regular outpatient home monitoring and I see hospitals as another. I see in-hospital care as another set of standards. What amazes me is the disparity that I am hearing about the way that this one small device is being used in so many

different settings and I am also somewhat surprised at the differences in sensitivity. I had never thought of neonatal before but that is certainly a class of its own.

I am also surprised at the differences in the devices themselves, the disparity and I think if we are going to talk about managing patients, we might have to talk about some more standardization of the devices. Each seemed to have different tolerance precisions and biases so I would see four, certainly three different sets of standards. And I think I will get to the other later on.

DR. NIPPER: Thanks. Dr. Habig.

DR. HABIG: Sometimes I have my industry representation hat on which is I guess most of the time my job here. Sometimes it just feels like I ought to make a personal comment. I am struggling with, kind of with the first two meeting goals for this panel compared to an august group like the American Diabetes Association or AADE or others who have already sort of counted on what they say the goals should be and I am not sure that we are going to do a really good job of answering or of satisfying the first meeting goal of identifying how patients are currently being managed. Obviously we have clinicians here who do manage patients but we are a small group of clinicians compared to

a consensus statement from the ADA relative to glucose meters.

Patients are being managed by being encouraged to monitor their glucose values wherever they are and sometimes that includes in the hospital so I think one way to answer the question how patients are currently being managed is they are being encouraged to monitor glucose to take multiple injections to maintain tight glucose control, the recommendations from the DCCT.

In terms of representing manufacturers, I think as a group industry is interested to know what goals of management and then several questions later, what are the specifications for monitoring devices. When we get to that part, I think we will be much more interested in and want to interact with this group and others on can we get there.

DR. NIPPER: Patients are currently being managed, I think one of the ways we can describe that is patient manage thyself. And that is not always a bad goal. Dr. Rosenbloom, we are talking about meeting goal number one.

DR. ROSENBLOOM: Okay.

DR. NIPPER: I just made a great leap. I didn't mean to wake you up.

DR. ROSENBLOOM: I was actually lost in thought.

I may have looked asleep but I was lost in thought, thinking that you were going to your right after going to your left.

DR. NIPPER: Would you like me, that sounds very chivalrous. Do you want me to go on to Dr. Goldsmith?

DR. ROSENBLOOM: NO, that is fine. I am ready. I think the, I agree entirely with what Bob said about how we are attempting to encourage patients to manage themselves but the reality is that, and I think we have heard a bit of this the past couple of days as well, that currently there is inadequate use, we heard enormous numbers, it sounded like the national debt on the numbers of strips that are being used but, and the number of meters out there but I think it is fair to say that there is inadequate use of self-blood glucose monitoring and inadequate quality control of its use in the home setting and it is typical that patients do not bring their meters in to be checked. They forget their meters or they don't want to bring them in because they don't want us to download them and see that they have done four blood glucoses in the past three months and so forth.

So I think that there certainly is an attempt to achieve the best control possible with the current methods available but that there is a great deal of under-

utilization and I think that one of the speakers addressed the point that the technology that we have is not being adequately used and if one looks at the DCCT in a highly motivated group of patients beginning with 10-year-old technology now, they were able to achieve a great deal of control in the feasibility phase of the study which was using the old white technology and under much more difficult circumstances so yes, the general trend is to improve control with the techniques available but the reality is that this is only now beginning to be applied to type two patients and is still widely under-utilized, particularly in the pediatric population and particularly in the adolescent population, it is much more difficult to carry these things through.

I think that is as specific as one can get but there are figures about the inadequate use as we have heard already today. What goals are appropriate for different groups of patient and different treatment regimens? I agree with the, I was concerned with the two groups because I agree that there are more than two groups. We have actually heard about five groups if one wants to throw in, wants to return to the discussion of selecting out a group that we are not really interested in individual blood glucoses on

but just in trends which was another group we heard about which I assume is a stable type two patient but that would be a fifth group and I don't know that we want to start thinking about different standards for all such groups but certainly the neonatal group and having even different calibrated instruments in the neonatal setting because that is really not a home use. One doesn't, there are situations indeed where we do send kids with neonatal hypoglycemia home for home testing but in those circumstances actually the technology that we have is adequate because we are just interested in knowing that they are under 60 or under 50 in most circumstances so I think that that is a very important group.

I think that it probably is more important that the unstable, that is, type one patient, totally insulin dependent patient probably has more of a need for accuracy than the relatively stable type two insulin taking patient or oral hypoglycemic taking patient. I would agree that there are at least three groups.

DR. NIPPER: Thank you very much. Dr. Kurt?

DR. KURT: I am interested as we get into this kind of Pandora's box as more and more ramifications of what we are being asked to do sort of unfold and I think in

answering the first question and identifying the patients, obviously we have gone beyond the home health care or the home use of the self-monitoring devices to a non-home category and I think perhaps all of the non-home categories could be lumped into another set and then subdivided so that you would have those used within the hospital or the medical offices, those used by home health care agencies, those used in a more hypoglycemic setting such as the neonatal intensive care units and that would be the second category.

I am also interested in since there is a difference in how each device works that patients be advised that not all devices are the same, that those used in, say, intensive care unit might be better of a certain type of device because patients might have the oxygen or are being shock, hypoglycemic for those related to glucose oxidase could make some significant difference.

I am also concerned in the category of reporting as we had yesterday through Sharon Dillard that there is an exemption that applies to a kind of a non-reporting category. On the other hand, I was encouraged among the industry reports that the industry keeps track of the strips that are actually being sold and knows how many devices approximately that are out there so we do have from the

standpoint of a voluntary reporting base the denominator there but on the other hand if the device that uses just the arm, the diosensor device exists where you have no track of the number of usages, perhaps it would be wise to have some kind of a meter in there that keeps track of the number of usages so you could obtain a denominator in that way.

I think the focus here should be on patient safety and patient education and the obviously the safety area was pointed out in part yesterday and again today, the concern of hypoglycemia being three times higher in the closely managed patient in the DCCT. And the, under those concerns a function of the devices and blood sugar levels below 75 I think should be emphasized and perhaps the manufacturer's devices could look into methodologies that could, say, have a secondary scale once a blood sugar level of less than 75 were reported that you would slip into either a different spectrophometric type of scale or a filter would apply or you average in so many reports or something else would apply and the emphasis for that also exists in the neonatal intensive care unit where obviously I think there is a market driven there for the device that would better report in the hypoglycemic scale.

The last thing that I am concerned about is that

the number of deaths that were reported yesterday and the adverse device reporting being 55 that obviously we need to keep track of this and that proper reporting needs to occur in the future so that this can be absolutely minimized.

DR. NIPPER: Thank you. Dr. Zawadzki.

DR. ZAWADZKI: I think it has become clearer and clearer that there is a significant distinction between the use of the meter in the home setting and the use of the meter in the hospital setting and that was very nicely delineated by our last speaker.

What is less clear to me personally is whether there needs to be a difference in the meter per se or whether the difference is really in the way we use and interpret the results that are obtained with that device and I think that is an important distinction because currently we are using the same technology in both situations and I must reflect personally from my view of the last 15 years, I think we will go a long way.

I remember using those big devices that were shown this morning, one device was available in the Joslyn Clinic when I was there as a resident and that one device tested every single patient at the hospital four times a day. So I think we really have come a long way from there to the

variety of meters we have available. Certainly there is a possibility that technology can advance further, I have no doubts. But I think a lot of our discussion has been more around the issues of how we use the technology, how we interpret it and how we adapt software, how we adapt standards and so forth. I think that distinction needs to be kept in mind.

The other issue that I wanted to raise is that we have been focusing on a document that is really meant for the purview of the manufacturing community and the FDA and perhaps some other professionals. What I think is really lacking is a uniform document to be in the, as part of the package insert. I have reviewed the package inserts for some meters and they vary in quality I think. Some are outstanding but there is a lot of variety in them.

I think it will be important to outline some of the issues that have clearly been raised as issues of concern at this meeting either by some of the speakers or through the discussions we had and it could be a very simple document that would be one or two pages that would, for example, suggest that the consumer and since this has been a consumer driven business, that the consumer contact the physician to compare the meter to a laboratory method at

least once a year or whatever standard is established, to explain glucose measurement variability in a simple way that we have been discussing at length here, to explain the limitations of laboratory methods let alone the limitations of meters, again in a simple way so that people are not frustrated when they are getting a reading of 250 versus 255 which happens frequently in my experience.

And that there should also be some mention of a reporting back. That issue has been raised time and again. We spent a lot of time discussing data yesterday that most people agree was gathered in a less than ideal fashion. Well, why not invite the consumer to be part in an active way of contributing data and that can be obtained perhaps with a little bit more reliability than is currently available.

MR. COOPER: I don't have any disagreement with anything anybody said. I may phrase it slightly differently.

I think in terms of how patients are being treated, we can all agree that patients are being treated in different ways in different situations and sometimes they are self-monitoring in their home. Sometimes they are being, these monitors are used in the hospital, sometimes

they are used in the clinic and sometimes they are used in other health providers' office. So there are a lot of different uses and some of us would say that there should be different guides for different groups and there might be three or four or five different groups and I would agree with that except I am concerned that sometimes patients in one group cross over to other groups and a patient, my patient who was a stable type two otherwise healthy adult has a certain kind of need but I can't guarantee that that person is not going to get in trouble sometime and maybe be in trouble and is going to rely on the meter to give different information rather than just trend information or small changes in insulin dose.

So I am worried that if we set up different, if the FDA sets up different categories, then I would want to make sure that the labelling for the category or the usage would be quite clear and that may not be too good for marketing because it might have to say something like this meter should only be used in stable patients who are not ill and all of the other possibilities that we would run into.

Absent that, then I would think that I would be a lumpner rather than a splitter and say that I would want, I would think the meter would have to be responsive to all the

different situations in which the purchaser might attempt to use it.

DR. NIPPER: Thank you. Dr. Goldsmith.

DR. GOLDSMITH: I agree with your statements of lumpers versus splitters but I still think that there is certainly value in looking at the different groups and maybe having a minimum standard for all of them and then additional considerations for some of these groups.

I actually came up with five groups, one would be the home use for patients where we use these results as a guide for their own monitoring, professional use as Dr. Rej had suggested, in the hospital where physicians really use this for treatment and in some cases acute treatment of patients and in the hospital setting recognizing that there is usually a good program established for quality control, quality assurance, et cetera, and perhaps an additional professional use category for outside of the hospital setting.

Dr. Nichols eloquently talked about the home care patients and I think that there is an awful lot of glucose monitoring going on by professionals outside of the hospital where it is used to spot check in the treatment of patients and then of course the neonatal category and the pediatric

category which could be separate as well are particularly looking at newly diagnosed patients with a lot of fluctuation.

The only problem that I had, Dr. Rosenbloom, you were saying that it really doesn't matter if it is less than 60 for the hypoglycemic patient. That is important enough. The only caution there is what Dr. Nipper had shown in his slide where that 60 really could be 45, maybe to 70 and then --

DR. ROSENBLOOM: I was talking about outpatient. I wasn't talking about the neonates.

DR. GOLDSMITH: Okay.

DR. NIPPER: Tank you. I have a couple. In talking about how patients are currently being managed, I have learned a lot in these last two days. I am convinced that in the need to and the quite appropriate need to minimize complications of diabetes, we have engaged in a system of trade-offs whereby the traditional role of the lab director in the central lab has been delegated to the diabetologist or the family physician who is treating the patient and watching over the glucose meter results and trained, highly skilled technologists who performed those glucose regimens is now the patient.

We have not done an adequate job in translating the information required to do a good job of lab directing and medical technologists' work to those delegates and to the extent that we have failed in that transfer of technology and scientific information, our patients are poorly managed or may be poorly managed. And we have seen the sequelae of this in a large number of poorly documented, very difficult to trace problems that allegedly have caused serious injury and some deaths.

That raises the issue to me that I am somewhat shocked that the industries represented here don't have bite marks from their corporate lawyers all over them, that they haven't tracked this problem and run it to ground. I would like to see that very much more thoroughly and completely investigated so that we have a clear understanding of who is being hurt, who is dying, and why and whether or not it is a result of use problems, technical problems, or whatever reason.

The instruments that we have seen used today are not, are amazing but they are not quite as good in performance as equipment that those of us who have used in labs for a long time are used to. That requires some adjustment in our thinking about whether or not the results

when properly deployed are adequate for good management of patients.

However, I think that in general the technology is being driven by the marketplace as well as by the professional establishment. It doesn't bother me that a group like this is sitting around talking about this issue because we are a strange amalgam of all sorts of information and I think synergy has happened here because we have a mix of good clinical laboratory and consumer and research skills around the table.

That being said, I am ready to move on to whatever number of goal we are on. I am not sure whether we have done two or one but I would like to know if we can talk about it all, what goals are appropriate for the splitters' groups in different treatment regimens. I don't know who wrote these questions and I am not sure what we are supposed to be doing.

DR. GUTMAN: I will take credit for that and let me give these --

DR. NIPPER: What would you like us to do there, Dr. Gutman?

DR. GUTMAN: Let me give you some specificity here? This is fascinating for me. I am not a member of

this panel and yet I am a member of this panel and you have analyzed this from a slightly different take than we had and it has been useful, just the concept of the way, I think the way the splitters are studying this apart and dissecting it.

There are a number, whether you decide you are going to lump it with a minimum standard for all of these products or whether you decide you are going to split and allow varying standards for different parts and that is actually a very important issue for us because one of the things we like to have here is some advice to the people who are like bio-control. Bio-control is not unique. A lot of people who are looking at alternative methodologies and one of the issues is are we going to be more innovative or more giving in terms of looking at those methodologies because we do recognize that accuracy needs may be different in different populations or with different uses or with new technology.

That is really an important issue that I would like you to all re-address at some point but what is floating around here, I tried to represent that and Dr. Parker also represented it in his handout is a plethora of performance goals. Everybody has a performance goal, one I never even heard of, the TNO guidelines I never heard of but

certainly I knew about the ADA guidelines, I knew about the NCCLS guidelines and I have come to know and love the Clarke-Cox guideline so there is lots of guidelines and I guess the question, I don't know that you have to decide right here at this moment what guideline fits every population but maybe could offer some general advice on where we move forward with either trying to sort things out or trying not to sort things out in terms of performance guidelines.

Ms. Rooks yesterday pointed out that there are guidelines and there is performance standards, voluntary performance standards and you can develop actual FDA driven performance standards. You can do it through consensus, you can do it by fiat. There are all kinds of different ways. Does anybody have any advice? The first speaker today gave me a sort of a target, 20 percent total error. I interpret that in the classic to mean bias plus two times CV and the industry person should correct me if I have misinterpreted that and then you just absolutely blew the wind out of my sails when you show that awful chart showing that what I thought was a perfectly reasonable target has really scary performance.

But I guess it would be really fun to hear, making

the two critical issues is should we lump or split and if we are going to lump or split, how giving are we going to be in terms of new technology and how do we move forward? I don't expect you to define performance goals for every possible use or even for all uses now but what you think a reasonable thing for us to move forward to try and pin that down or should we give up and not try and pin that down and leave a sort of laissez faire, Arabian bazaar type environment.

DR. NIPPER: The quick answer to your last question is please don't give up but on the other hand, I don't think we will be able to bind whatever comes out of this meeting in leather and put it on the shelf as the final form. I appreciate and I hope I am speaking for the panel, I appreciate being asked to help you. That is all I think I am going to do today and if more of what I say is helpful than confusing I think it will be a good meeting for me because today, from my standpoint, I believe I have learned a tremendous amount and I think in a way I kind of need to walk away and read some of these standards that Dr. Parker talked about and others and think about this some more, maybe talk to some of my trusted clinical colleagues and so forth and maybe have at it again.

I am not looking for homework but I think it might

not be a bad idea. I would like to know how much detail and how specifically you would like us to go each question by question here or whether some of our general comments have sufficed. Do we need to come back and talk about specifically, identify areas where we can work together? Skip to question five, in other words?

DR. GUTMAN: Yes, I don't have delusions of grandeur for myself or for the panel. I like the idea of giving you not necessarily a homework assignment but certainly an opportunity when the dust settles to put all of this together and perhaps to submit in writing. We might regenerate these five questions in a week or two once the dust settles to give us an independent appraisal of where you think we ought to go with these different items.

Again, if somebody is really feeling daring and wants to be provocative and drive us, I am not opposed to that. I would delight in that but that is not a requirement, that you are to give some general direction and our hope as a follow-up with this is to be a little more interactive with the industry and make them help us resolve some of these problems.

DR. NIPPER: Well, for example, one of the things that I thought about that I thought was a really interesting

target to think about was the number of plus or minus five percent total error was mentioned today as a goal that had come from one of the consensus groups. I forget which one. ADA. And I thought to myself that that settled in pretty well with the idea of being a lumper and seeing if industry could make that instrument and use it basically the same way the current instruments are being used now but the big question mark, of course, that arises from that is whether that instrument can be engineered and manufactured without bankrupting the device industry that is providing it.

So you see, we won't know some of those things until we start kind of kicking them around among the various groups but to me that seems like a reasonable place to start thinking about compromise, to crank it down a notch or two to try to get as good as we need for the current uses. Let's see if we can improve the utilitarianism of the instruments so that the user can, so we can get rid of some of the use errors. Let's ask industry to cooperate with the FDA to even a greater extent and try to track some of these serious problems down, run them to ground and find out what is actually going on here because I think it is potentially dangerous and I am not talking about in a human, dangerous to human beings but I think it is a very sensational number

to throw out there and taken without the caveats that the data is very faulty and very unreliable could be explosive so I would like to see industry work on, let's work on that issue.

I think our biggest goal from this should be better patient education. If I take away one thing from this meeting, it is from the diabetes educator who spoke, our Kansas lady, Debbie Henson, that that is where we need to put our money. We need to make better medical technologists out there out of those patients.

DR. BOUGHMAN: I would like to raise a different type of issue that I have been thinking about since yesterday. Having been on this panel for a while now, having been presented with different 510-Ks and having looked at a lot of data, I don't know how many inches' worth over the years, a new problem has arisen and even before I start thinking about plus or minus 15 or 7.4 or 5 percent or whatever I might be thinking about, we have a new basic safety and efficacy problem facing us or the FDA does and that goes beyond the pre-market evaluation of a single test strip and a meter that are presented as a coupled pair.

Having asked some fairly what I thought were naive questions and apparently some of the other folks around the

room were now aware of this, a 510-K comes in and you have a meter and a test strip and that is considered a device, part of the same system. However, there are test strips out there that are presented for use with other meters and when that test strip comes in, the test strip alone is a device that is then evaluated as a device in and of itself. Then if one of the test strips that was presented as a part of a coupled device is marketed for use with other meters, that strip comes back in as a separate device.

So the next level of safety and efficacy that we have deals with the concept that at least many of the diabetic patients I know and in fact, those with other kinds of chronic illnesses are basic survivors. They are clever, they are creative, they are adaptive and, in fact, all of a sudden we are being asked to step back and assess the safety and efficacy of possible uses or combinations of uses which to me opens a very different set of issues unrelated to the data that we might examine pre-market in a 510-K proposal on the table before us.

And I am not sure exactly how to fill that gap nor where we might get the data and that might come out of question number five, in fact, with how we could get industry the patient groups, some of these associations

working together with the FDA with some broader studies to really look at some of these issues but I think there are monitoring processes on the, with the new regulations that are being implemented on June 1 for the quality control side but we don't have that same parallel safety net, if you will, post-market on the peer device and the strip side which really adds a complication to the whole picture.

DR. NIPPER: I think you did a great job of question number four. That helps tremendously.

MS. LAPPALAINEN: I just wanted to make a comment as one of my other capacities in DCLD is I am now the interim branch chief of the clinical chemistry, toxicology and hematology branch and I just wanted to say from the standpoint of the submissions that we receive, we receive all kinds of submissions. The FDA does not tell a manufacturer what to submit as a form. In other words, you must only submit the meter, you must only submit the test strip or you must only submit the QC. We get them in all shapes and sizes and it is one of the reasons why applying a guidance document to the manufacturer, there is frustration on our part and on their part and I think it is very understandable because of the variety of the submissions that we do receive. That is about all I wanted to say on

that.

DR. NIPPER: Ms. Rosenthal.

MS. ROSENTHAL: Are we addressing question four because I would like to add something to that.

DR. NIPPER: We sort of are addressing questions one through five at this point I think. I didn't get a clear answer from Dr. Gutman about whether we should go in sequence and so I am going to go in whatever sequence we want to and so we will have open discussion for a while and if I see that a remark seems to apply to a question, I will do like I did with Dr. Boughman. So jump in, the water is fine.

MS. ROSENTHAL: The other thing that struck me in all this conversation is the calibration is clearly a problem. Ken Ervin mentioned it. He said it was the largest number of complaints that result in improperly calibrated devices. Someone else mentioned it. Jim Nichols I believe it is mentioned that there were differences in the calibration. It strikes me because I can remember using those very large glucose scanners that were just passed around.

IN the beginning we first of all while they were big and they were ungainly, we would calibrate them and then

we used one set of test strips. When subsequent test strips came, they were calibrated to the same, they were calibrated the same way. We didn't have to calibrate to that test strip. I am a little confused why the consumer has to adjust for each bottle of test strips, case of test strips that is manufactured. Can't the manufacturers try to be more, try to manufacture test strips that can match the calibration so we don't have to keep recalibrating. Does that --

DR. NIPPER: Look to your left for the answer to that question. Your immediate left and your far left.

MS. ROSENTHAL: I think that is something that maybe the manufacturers want to discuss with one another, trying to have some kind of regularity in the test strips. Also, when you calibrate with a solution, that is an ungainly procedure in itself. It falls victim to the same problems that blood testing falls victim to. If the procedure is incorrect, then the calibration is incorrect. It would be very nice to not have to ever calibrate frankly with a wet solution. It would be very nice if way in the future it is really much sooner if we could possibly have an internally calibrated device so that we don't have to put a stick into it and so that we don't have to worry about the

elements getting to that stick or our procedure being incorrect or putting in the wrong code. I think we could use some uniformity in that.

DR. NIPPER: You see, that is why it is nice to send the blood to a central lab because you let us worry about that. The problem is it takes you too darn long to get the result.

MS. ROSENTHAL: Right.

DR. NIPPER: So if you want to do it yourself, you have got to do what you got to do. That is the problem and that is one of the things I was referring to when I said that we, in order to redesign, re-engineer these instruments so that the human factors are a little better and so that there is less work, less laboratory technology type work, I think it would help tremendously. I would concur with you.

MS. ROSENTHAL: I guess that is what I am saying. The less human interaction the better. I mean, we will need a person for their blood but beyond that it would be nice if you could just --

DR. NIPPER: Maybe you won't even need the person for their blood one of these days.

MS. ROSENTHAL: That would be wonderful, of course. We would all hope for that. And there was another

thing that I noticed, the silence about it is deafening is the only way I can say it. Nobody has talked about the auto-letter, what I call the auto-letter, the lancet device which is the number one step and as Beverly said this afternoon, if you don't get a good pap smear, you don't get a good result, no matter what. If you don't have a lancet that gets a really good drop of blood, it doesn't matter what you do with that blood, it is not going to give you a good result.

And it occurred to me when we watched the video of the two children, I wasn't surprised that one came back okay and one came back incorrect. Maybe she took the blood. Maybe she used the same device but she didn't use it the same way. Something that very commonly happens to diabetics is they will prick their finger and they won't have enough blood so they squeeze it and what then are they getting. I was speaking to Murray Lowe, hello, Murray who is sleeping over there. He has a son with diabetes and Murray said his son has a device that has a little cup in it and his concern is that he doesn't fill it with enough blood so he squeezes it.

You don't get a good blood sampling when you do that and it occurred to me that maybe somebody would want to

think of a lancet device that hooks onto their finger a little bit so you can't pull your finger away so that you get a really nice, substantial drop of blood and I think that has to be integrated into this whole system. If we are going to integrate the patient, then I think we have to integrate it from step one.

DR. NIPPER: All of these comments.

MS. ROSENTHAL: And one caveat. I was a splitter but then I was thinking I could be a lumper with paragraphs so we might want to think about it like that, too.

DR. NIPPER: Does anyone from industry who heard Ms. Rosenthal's plea, Dr. Habig gets paid the big bucks to come sit on the hot seat, but he may want to look out for somebody else out there who will handle it. We have got two. How about five minutes?

MR. PURDY: Five is fine. I hate to brag but this is one of the things we have been very worried about and that is the main difference between our device and a great glucometer. Obviously we still have a lot of a ways to go -

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DR. NIPPER: I know who you are but the tape doesn't.

MR. PURDY: I am David Purdy, president of Bio-

Control Technology and we are developing the Diosensor 1000. Our system, in answer to Dr. Kurt's question, does record up to as many months of data as a patient wants on the PC-MCIA card and the physician merely has to take out the card and put it in, either we can load in the data or in his office he can take the data and he would have a complete record of however long he would like to have along with the reading and the date which are recorded and the patient, of course, can recall that data.

Now, with regard to calibration, we have a calibration built in, I am sorry, not calibration, we have a control sample built into the device so that before each reading it reads spectorally a sample that looks just like the tissue of the arm and in it is 100 milligrams per deciliter. In that machine is an algorithm which operates on this control sample and if it doesn't read the control sample properly then it will tell the patient that the device is not functioning properly and to return it to the manufacturer. So these issues that you are discussing here, every one of them is taken care of by these two mechanisms.

DR. HABIG: I will take over for the chair at this point and suggest that Mr. Duncan might come up and make some comments as well.

DR. NIPPER: You are just made because you couldn't chair your meeting in Baltimore.

DR. DUNCAN: I am Dr. Lou Duncan of Life Scan, standing in for Ken Ervin who had to catch a plane. I am a principal scientist in our advanced QA group. Your question about calibration is very well taken but when you send a sample to Dr. Nipper's lab, to his \$100,000 or \$200,000 instrument, he calibrates that every day.

DR. NIPPER: Once every three months.

DR. DUNCAN: Once every three months and then you are using a solid state device like we do.

DR. NIPPER: Then I use controls every day.

DR. DUNCAN: Then you use controls every day. And he is doing that as long as he uses a single lot of reagents. If he changes a lot of reagents, he has to recalibrate. We are attempting to bring you as much consistency as we can in our case about 90 percent of our reagents fall within three of the calibration codes and another 10 percent fall outside that to match up all of the millions of strips, actually the millions of meters and billions of strips together to give you that answer which is being driven inward means that we have to allow for certain variances and to calibrate this as carefully as possible we

have to give those calibration codes to give you the accuracy.

I understand your concern. We are working at it but there isn't a simple answer to that yet.

MS. ROSENTHAL: You said you calibrate. Could you give me those percentages? You said 90 percent calibrates what, three different codes?

DR. DUNCAN: Yes, and then 10 percent fall outside.

MS. ROSENTHAL: And how many do you have altogether?

DR. DUNCAN: We have 16 codes.

MS. ROSENTHAL: No, no, but I mean, how many strips do you, would you say that you manufacture?

DR. DUNCAN: We manufacture several thousand lots a year. Each lot contains several hundred thousand strips and within those they all have the same calibration code.

MS. ROSENTHAL: So if you can do that for several hundred, and I am not, I am putting you on the spot but I am just sort of suggesting if you do it for several hundred, how come you can't do it for several hundred more?

DR. DUNCAN: We are doing --

MS. ROSENTHAL: You have the technology already to

do it.

DR. DUNCAN: I would have to have a statistician answer for me but I think statistically we are virtually doing that. In other words, when I say we get most of them within those three codes, we are getting a central one plus or minus several standard deviations and what you are doing is you are really looking at the statistics when you get down to it. We could broaden what we mean by a code and achieve what you want. That would give you less accuracy. To get the accuracy you want at this point, perhaps the process won't satisfy that.

DR. NIPPER: When he broadens it, it makes the between lot variation look very big and if you think there is something wrong with the machine when what it is is just a different lot that is giving you information.

DR. DUNCAN: Yes, so bottle to bottle we are quite good and then lot to lot we wish we were better.

MS. ROSENTHAL: So are you working on it?

DR. DUNCAN: Of course we are. So is everybody else.

DR. REJ: This is also following up on question number, on number four. It seems there are an awful lot of recommendations - five percent, 10 percent, one milimill per

liter, 15 percent, 20 percent. My brother is a physicist and he says the difference between physics and chemistry is that in physics 1 equals 10. And to me, 15 and 20 are pretty close and actually I am more impressed that the, how close all of these recommendations are rather than their differences. Sure, the number is different but basically it looks like 20 percent, plus or minus 20 percent total error, 95 percent of the results fall within that error, error margin and that is the state of the art for basically all the devices.

Dr. Parker did a very nice job in summarizing all of these and I would say at first blush that a recommendation to the FDA is that any new devices or any other devices that come to you that regardless of the technology if they are way outside, plus or minus 20 percent, they are not substantially equivalent to what is being done. Very practical recommendation. That is my first blush at this.

Certainly the diabetes association have a goal of five percent. It is not a performance standard. It is a goal and a goal should be plus or minus one percent. Now, if everybody could do that cheaply or that patients could easily afford it and the manufacturers can make a profit

from it, then there would be no argument about it but it seems to me that 20 percent is the current, is what we are living with and then to broaden that further doesn't seem to me to be even in the best interest of anybody other than the manufacturers, the physicians treating the patients, the patients or the FDA to relax the current state of the art much beyond that.

DR. NIPPER: I would agree with you, Bob, and Ann, too, that if you add to that that the goal for the manufacturers, the physicians who treat the patients, the patients and the regulators would be then to try to maximize by whatever they are supposed to do fulfilling whatever role they have assumed, maximize the number of patients who achieve plus or minus 20 percent because my feeling is that what our problem is is part of the time the device is being used in a setting where the plus or minus 20 percent is not good enough and that may be an off-label use.

Part of the time it is being used appropriately and correctly by a well-motivated and well-trained patient and physician and its on-label use is perfectly okay and then the third group is people who are not using the device correctly for whatever reason and don't have adequate access or have refused appropriate training and then suffer

consequences as a result of use errors. I don't think and that is why I am encouraging the industry to jump in these really adverse reports, I don't think that most of the problems we are seeing are as a result of inadequate technology or manufactured products. I think they are, the system problems where the patient is in the system and that is what I am guessing. Dr. Habig?

DR. HABIG: I have got some notes here that I would like to provide some input to several comments that have been made including the ones by Ms. Rosenthal.

But something you just said triggered something from maybe Dr. Rosenbloom said earlier about how come there are not lots of, well, 55 at least, lawsuits on the issue of product liability. It might have been Dr. Kurt, I am not sure. And you just said industry needs to chase down the incident reports that allege death and serious injury.

DR. NIPPER: Maybe I am just paranoid but if I were industry I would want to chase them down.

DR. HABIG: Well, you said it almost as though you don't think we are already and that is one of the impressions I wanted to correct. Our product liability lawyers in industry are also concerned but the fact that industry has not been put out of business by lawsuits or

successful lawsuits alleging or proving that the device contributed to death or serious injury kind of makes my case that I described earlier that the reporting system that the statute requires doesn't allow much interpretation, in fact, doesn't allow any interpretation so the reports are made because the regulation statute require it.

I think there are, I think it is inappropriate to assume because there are deaths that they were caused by the device. I guess I said that earlier but it may be it is worth repeating.

From an industry viewpoint, I may have said this earlier, too, if any of us were able to create a system that was inexpensive that we could make money on, that customers could use, that would be at the five percent or even better, you know, rolling all those things together, it would have already have been done. Nobody is back there saying gee, I think I will wait for the other guy to do it so they put me out of business. If we could do it, we would do it.

Specifically to Ms. Rosenthal, why don't all of the strips come out the same? Why do I have to worry about different button numbers. It is again the kind of state of the art of technology of the variety of technologies being used in the way strips are made. It is not as simple as the

analytical chemistry that we would like it to be where you could weight something, put it into a flask, dilute it with pure water and know exactly what you have. The technology is simply not good enough and if when the person finds the technology that is good enough, they will do very well because if it is discoverable, it will be put into practice.

From a general industry standpoint, we talked about actually a bunch of times that industry seems to be a kind of one thing and I would like to remind the panel that we are all competitors so when we say industry and why don't you, it is not quite so easy as it sounds when faced with this kind of panel meeting, it looks like industry is all sort of together and in this case I think the industry is all a bit nervous about what could be improper or inadequate conclusions from David that we are looking at, that the FDA is looking at that would drive more proscriptive requirements or forced standardization of methods based on the assumption that there is a problem and I don't think we believe there is a level of problem that suggests we need more proscriptive standardization or forced, more difficult hurdles to clear in order to get products to market.

I think the thing that encourages us the most is that Dr. Gutman has allowed, Dr. Nipper you have also said,

we ought to all get together and work on these issues and continue to interact with each other either in this form, under the aegis of this advisory committee or in other forums to find the best ways to get to where I think everybody would like us to be to have devices that contribute to optimal care of diabetes.

DR. NIPPER: I would like to respond to one thing you said and then I would like to declare a brief recess because it has been almost two hours since we started and I will tell you what I think we should do afterwards and see if that sits well with the panel.

One of the things that I would like to, I would like to respond to your remarks, Dr. Habig, about is the perception that was left in this group by the discussion of the number of serious problems in the problem reporting system. I would not want anyone to leave this room or to look at this tape or hear this tape and think that I believe that these devices are killing people at the rate reported to this group in the reporting system.

There were adequate asterisks attached to that data in the presentation, so much so that I don't trust it but I also know from working in clinical labs for 25 years that any time I put an number in a chart and put an asterisk

in it, the numbers survived and the asterisks did not and the footnote got lost and was ignored by the people who read the number and the number many times got acted on, sometimes inappropriately.

So I learned a long time ago never to put garbage into a chart and assume that someone would look at my caveat and say well, that probably was a bad number and I probably shouldn't use it but it is in there.

I think this is the same quality of information and that is one of the reasons it frightens me. It frightens me that these numbers may be used for purposes totally inappropriate and to that extent, I think you and I are on exactly the same wave length.

I believe that your product liability lawyers in the industries that are represented who make this product are right on top of these problems. I believe if there were a problem, if there had been a problem, it probably is corrected and done but nevertheless these reported problems survive and surface in public fora like this so that is why I am kind of surprised that there hasn't been a bent way to deal with these issues in such a way that we have better data report in public fora such as this.

So I would, that is one of the reasons I am

challenging the industry to deal with this issue because I think it is a housekeeping problem but it could be a tremendous, it could add to the public perception that there is a significant problem with this segment of the diagnostics industry. I hope that helps you understand why I was bringing it up. I am wishing the best for the diagnostics industry not thinking the worst.

At this point, I think we could all use a stretch, particularly after that remark and what I would like to do, after consulting with Dr. Gutman and the executive secretary is I would like to move to meeting goal five and do that with a round robin and then I would like to help our former executive sec., Ms. Rooks, in dealing with three questions that she asked in her presentation and Sharon will put these up on the panel, on the transparency. We will go around the room, let each one do that and then Dr. Gutman will unlock the doors and we can leave.

Before I do that, though, I want to recognize the fact that there are some FDA staffers here who may want to ask questions of the panel. If you would like to do that, we will certainly entertain those and we will also entertain any comments from the audience if you can stand to stay with us that long.

So could we do it in 10 minutes? Start on question five.

(Brief recess.)

DR. NIPPER: We are getting a couple of people back to their seats. In the interests of time, I would like to begin a round of panel to identify areas in which the agency professional groups, patient and manufacturers can work together to help achieve the various goals for glucose monitoring and contribute to increased quality patient outcomes.

In particular I would like to add my own subquestion to this. Parenthesis is there a role here for NCCLS, close parenthesis. That might take care of the, that might be a good umbrella. We have already seen a document cited that deals with POLs and near-patient testing, DUP-30 something or other dash two I think it is. Whatever. Anyway, Dr. Habig, do you think you could get your warring tribes together under the NCCLS umbrella to work with the FDA? Or is there a better way to do it?

DR. HABIG: I think, I hate to say it is a better way but I think I would propose two parallel routes.

DR. NIPPER: Other way.

DR. HABIG: Other way, there you go. I think the

agency and industry with the help of the professional organizations and patients ought to be able to work together to create whatever the next stage of guidance documents or documents is appropriate. It sounds like the agency is willing and eager to do that and I think all of us are as well.

The reason I suggested that that particular thing might not be under NCCLS is because it is a guidance document which, while it doesn't have full legal regulatory bearing, it casts a very large shadow. And where NCCLS may be useful would be working with professional organizations like ADA and AADE to refine the performance goals, perhaps some of those goals might be segmented as Dr. Rej described to say five percent is required for near patient testing for some of those kinds of uses of the technology whereas self-monitoring at home might have different goals.

So I think an NCCLS umbrella could well fit over a goal setting kind of approach, NCCLS creates guidelines and standards and as I said earlier, industry is quite a bit nervous about proscriptive standards but guidelines and goals challenge us and have challenged us and I think we are willing to accept those challenges as fast as we can figure what technologies will be available to meet them.

DR. NIPPER: What areas do you think we need to work in besides the guidance document? In other words, do you think that covers all the areas that you would like to see that synergy between FDA patients, the industry and professional groups?

DR. HABIG: I am focusing on that because it is the mechanism by which the agency tells both its reviewers and the sponsor submitters to follow things which make reviews straightforward and in fact easier for the reviewers to handle so that seems like the first area and, in fact, nothing else comes to mind right away to what other areas of cooperation would be useful specifically when we are talking about the agency.

DR. NIPPER: In particular I like the idea of bringing in professional groups other than laboratory into the mix because they form an important part of the people of the mix of people who use the instrument both in a professional way and as patients. I also like the idea of bringing in the diabetes educators. In case the tape didn't get that acronym, I like that very much.

Anything else?

DR. HABIG: That is all.

DR. NIPPER: Ms. Rosenthal, how would you answer

question five? Doesn't have to be different than Dr. Habig.

MS. ROSENTHAL: Well, I do first want to make it very clear to the industry that when I pose that challenge, I am not saying that they are not doing a wonderful job. They have certainly taken us quite a distance from where we were 10 or 15 years ago but it is a challenge to try to be a little more uniform. I still would like to see some focus on the very, very first step which is how to get a good drop of blood. That is an okay goal.

DR. NIPPER: Thank you. Dr. Harrington Falls.

DR. HARRINGTON FALLS: One area, not so much a professional group but just in general, public health and access to care because if we can get more people screened and the devices are available and people realize exactly what we are testing for is an accurate or a range, a qualitative or quantitative result, then I think we can make significant improvements to quality of patient care.

DR. NIPPER: Thank you. Next.

DR. BOUGHMAN: Maybe it has just been a long couple of days but I have felt some at least frustration if not feeling a little upset a couple of times when various people have suggested what we ought to be doing. And I am very used to being on the hot seat as the purveyor of all

university policy to students, staff and faculty and the keeper of the regulations, as broad as they are, throughout a university and I understand that sometimes message and messenger get mixed up but there is a job that we have to do as a review committee and in conjunction with the FDA as a regulatory body to, in fact, sometimes protect people from themselves and that has come into contrast with several other requests that have been made of us.

For example, to identify human factors that may be important, to determine the patterns of use and the patterns of error of use and several other different aspects especially related to the human factors and in fact even one of the presenters suggested that cost was a human factor.

Well, in fact, those are not at least what I consider my job as a member of a review panel. What I would like to do is throw some of the responsibility back out to the combination of people represented in question number five and say that if we do work together than I think we can gather, we all together can gather data on some of these human factors that are of importance. In fact, it is the patient groups that would represent the individuals who are using these devices and could come up with those lists of factors that were important to the users, not my guessing

what is important or asking a handful of patients that I have interaction with.

So I think we would need to work together, especially on the human factors issues determining the reasons and the patterns of error and those that are important for those who are monitoring for trends and/or responding or are responding to individual sample results. And those might be very different but I don't think we really know that yet. We keep, we have at least a fruit salad here. It is not just apples and oranges. We have at least a fruit salad and may have some other things thrown in, too, so I think that there are some studies, there are some data that could be collected together with the manufacturers, with the patient groups and with the help of various oversight bodies.

The second major area that I am only going to initiate because I think we will come back to this later is that I think it is going to take everybody working together to, in fact, even broach the subject of appropriate information and educational processes to go forward for the users, for the health care professionals, for family members, for, and I consider manufacturers in this milieu as well, needing to possibly understand even more about the

disease than some might at this point in time.

So I think that those are two of the major areas in data collection and education strategies.

DR. NIPPER: Thank you very much, Dr. Boughman. Dr. Rej, are you going to be a lumper or a splitter here?

DR. REJ: Maybe a little bit of both. I am not sure that in meeting the goal of question five is to achieve a goal and to me the goals are really straightforward. Those numbers in terms of accuracy and precision just can't be low enough and that is a goal. Whether we achieve it or not and at what cost that is incurred by doing that is the question.

I wonder if maybe that should be rephrased to be minimum performance standards rather than the goal because I think the goal should be something that is basically a challenge to the technology. Dr. Habig said if we could have total error of plus or minus five percent, it would be there now so is a goal that is certainly worthwhile and if there are reasons to go for that, we should shoot for that but I think in setting realistic minimum performance standards for all of those devices, that would be useful to the industry especially for new technologies, perhaps non-invasive technologies as well, that there is a certain minimum level

that will be accepted and in that mix in setting it should be both clinical and analytical criteria, not merely correlation coefficients, not merely patient outcome. A reasonable mix of both of those.

And area that I think that this mix of individuals, whether it be NCCLS or a group, a consensus conference, held by FDA or another panel meeting, I think one area that would be fruitful for this sort of discussion is the area of quality control of these devices. I was impressed that I think everyone's expectations of a laboratory test, whether it is done in the confines of a laboratory or not but a laboratory test done in a medical institution such as a hospital, I think the expectations are that those need to meet and are being performed at a higher standard than by an individual in his or her own home even though they have a much greater vested interest in the quality of that result because it is their life that they are managing.

But it came clear from this meeting that probably the reverse is actually happening, the mix in a large institution, a mix of hundreds of operators with hundreds of devices, probably consuming strips and numbers of lots of strips at a much higher rate than an individual and that the

need for an increased quality control regimen even though it is the same box in that setting is probably necessary. Not only desirable but really necessary.

And I think that because of this status of such devices being on the CLIA waive list, I think that adds another interesting mix to the equation and I think that a mix of government agencies, professional groups, the lab folks and clinicians, patient and manufacturers, could probably address that in a reasonable way and I think there needs to be a very, very flexible quality control standard, something that is really useful for the individual diabetic in his or her own home or the parents of children with diabetes so that there is something that is really useful for them not necessarily the same standard for a professional setting.

And lastly I would like to underscore the chairman's remarks regarding bringing the diabetes educators into this because clearly the patients are part of this mix. It is usually patients are not part of the NCCLS grouping of industry manufacturers and professionals and I think that by bringing them in, that enhances their role in such a group effort to look at this particular class of devices.

DR. NIPPER: Thank you. Dr. Goldsmith?

DR. GOLDSMITH: I would agree with Dr. Rej's remarks with respect to including the nurse educators and also with Dr. Boughman's with respect to the patients themselves. I think any of the users, including nurses, we were talking a lot about the NCCLS documents and Dr. Habig and I have been working on a specific document relating to point of care testing and in creating this document we very much relief upon the nurses who actually do this test in the hospital setting. So I think that the users really need to be involved.

As far as specific issues, again I think Dr. Rej had just mentioned it and I mentioned it earlier. Quality control, I think that needs to be addressed specifically. Certainly lower limits, we talked about that earlier. How can this be achieved and what will it take to make this happen? How can we reach those goals and I think maybe one approach might be that the FDA, as they did in their guidelines identified specific issues and after convening a group of individuals that represent all of these users and the manufacturers, et cetera, identify these issues and then ask for specific feedback. I think if you ask for specific feedback and quantify it in a way you will be able to get a little further ahead with this.

MR. COOPER: I have a question and a comment. Can I do the question first? With respect to the question number five, I accept that we can substitute minimum performance standards for goals. Dr. Rej's suggestion I think is fine but are we talking about ways to achieve minimum performance standards to setting those or reaching them. Is the point of this question to identify areas in which all of these groups can help to achieve the setting of minimum performance goals or how all of these groups can help to achieve reaching minimum performance goals?

DR. GUTMAN: I don't think that the items are excluding.

MR. COOPER: Both.

DR. NIPPER: Either/or.

MR. COOPER: Okay, because they are separate tasks.

DR. NIPPER: Yes.

MR. COOPER: Then I endorse the concept of groups together, the groups that have been mentioned, especially including consumers. I would also endorse the besides diabetologists, the inclusion of family practitioners, general internists and geriatricians because, in fact, most people with diabetes are cared for by various kinds of

physicians and I would ask that one of the tasks of the group, however it is put together might be to identify areas of research that are critically needed because clearly you will be, the group will be looking at issues and scenarios and will be amazed at the lack of data to answer specific questions and if the group can then identify how important it is to answer that question and sort of rank priority about key or critical research issues, then perhaps other organizations can pursue that and help to fill in the needed information which indeed would help to set performance standards and help to achieve them as well.

DR. NIPPER: Thank you, Dr. Cooper. Dr. Zawadzki.

DR. ZAWADZKI: I would like to mention two suggestions or more specifically that have been previously made. I would like to see a prospective collection of adverse events by the major meter companies for a six month period at least, just to begin to address the question that we have been raising in the last two days and secondarily, I would like there to be a more uniform description regarding the concept and the goals of monitoring included with each meter, either as a separate statement from the FDA perhaps or as part of the information that is given in various forms by the manufacturers.

DR. NIPPER: Thank you. Dr. Kurt.

DR. KURT: I would say that at the end of the afternoon my answer is going to be nip and tuck as regards Dr. Nipper because I have an airplane to catch at the end of the afternoon. My concern is that there is a kind of constantly changing environment as the devices and process improves, it requires I think a kind of continuing review so I am hesitant to say that we should establish QC or performance standards that are written in stone. Because of that, I would like to use an example of the U.S. PDI, the United States Pharmacopeia Drug Index where I serve on one of the review committees where those are updated on a frequent basis. They are sent out to members and you review them annually and the U.S. PDI is printed with updates every year so a kind of review process that would be updated I think would be helpful.

I think focusing on certain areas such as the problems related to hypoglycemia, related to the DCCT, closely controlled patient where that occurs three times more frequently, about the hypoglycemia that occurs in the neonatal units because those can result in the serious problems that lead to death and should be an area of concern.

As well the adverse reporting that probably relates to hypoglycemia and what is actually causing that to occur, really looking into those cases that are the serious ones that are resulting in death and looking at those in depth I think is in order so that instead of sweeping it under the rug or taking the ostrich approach, because perhaps really some constructive measures that would correct either educational methods, it is not necessarily a device problem but perhaps something in the education, perhaps something in the calibration procedure, et cetera, really needs to be looked at from that point of view and I think it would be interesting to include within the, in question five in the groups, parties, patients and manufacturers, perhaps for the manufacturers to consider, to include a kind of consumer group and their input as to their labelling and education programs.

Not necessarily consumers at law but perhaps an informed consumer such as Ms. Rosenthal who certainly has a statistical and mathematical background in dealing with problems of this sort as well as having the family experience and including the large organizations such as the American Diabetic Association and to the editorial process, some kind of a delphi review where they at least have a kind

of preview or pass over process and then be involved in that kind of editorial process, few of us likely to adversely criticize something that they were actually involved in writing themselves.

DR. NIPPER: Thank you. Dr. Rosenbloom.

DR. ROSENBLOOM: Looking at the areas in which these groups should be working together, I think they noted most of the things that have been discussed. I would like to just review them with my particular perspective.

I am assuming, as Dr. Habig has emphasized, that we have the best technology that the competitive environment provides currently, that if it were possible to be more precise, more user friendly, they would be, somebody would be doing it. That is possible and they will be doing it I am sure but I think it should also be emphasized that these developments are done with a great deal of consumer input. I was just talking with one representative who told me about a year of testing their latest addition to the technology, their contemporary model in the field, color buttons, ease of use and all of those things so they do have considerable consumer involvement.

I do not know whether the labelling is as intensive as you suggest but certainly the use of it. But I

think the setting of the standards for accuracy is at one level, that is, the level of accuracy of the device used in an optimal setting and perhaps that should be the standard for in-hospital use but then we have to look at another level and that is what happens when this is out in the home and I know that the manufacturers are doing a lot more testing in that setting currently at considerable more difficult and costly but essential. But I wonder what the difference is and there is where the groups need to be working together obviously to get that data, what the difference is between testing in the laboratory or in the company for the accuracy of the system compared to the gold standard and the accuracy when in patients' hands.

Then having set those standards, then I think we need to consider the full array of products that are out there and whether all of the products that are out there are really appropriate for peoples' needs. That sort of flows into looking at means to reinforce quality control in home use and what kind of newsletters, recalls, information given to people who are buying strips to contact the manufacturer for the latest information and so on. I think that we need to look at that as a combination of agency, professional groups, patients and manufacturers.

We definitely need more data on adverse events but I would say that that is not purely an industry problem but that the agency also has to work on that and perhaps professional groups as well need to emphasize the importance of getting information in about adverse events.

I have in the past 15 years reviewed perhaps 100 cases of death in children with diabetes or with hypoglycemia unrelated to diabetes, delayed diagnosis and so forth and I haven't seen a single one that is causally related to erroneous blood glucose measurement by these devices and I would have expected that that would have come up especially in the neonatal hypoglycemia situation. Where I have seen problems is that they have detected the hypoglycemia but nobody has acted on it. So I think we really don't know that we have got a problem.

This is what I am trying to say and I suspect we don't. I think what has been described is associations but not causation but we really do need, I agree also that we really do need that data because it is, what we heard is dynamite and I agree with Dr. Nipper in that regard.

So I think we have a number of areas that we need to be working together on and gathering data that we can make some decisions on. I share the frustration that has

been expressed that we know what the questions are but we can't define either the problem or the solution until we have more information.

DR. NIPPER: Thank you, Dr. Rosenbloom. I have some brief comments about my opinions about question number five. I continue to turn over in my own mind some of the points that Kimberly Trautman brought up today in thinking about quality systems regulations. I think that is a fertile area for speculation and thoughts but it led me to analyze the various goals of glucose monitoring, that phrase, in a little more detail and I would like to see cooperation between government and professional groups, patients, and manufacturers in three areas.

One is design which was what prompted me to start thinking of this way and in these areas of course we can think about improvements to current designs, ways to dovetail in future technologies and ways to evaluation future technologies and so forth and that may or may not be an area that we can get great cooperation because of professional jealousies and corporate responsibilities.

The second area I would like to see cooperation is in performance. What I am speaking of there is the performance capabilities of the instruments, in other words,

will they work as they are supposed to when they have that good fingerstick that Ms. Rosenthal talked about when the lot to lot variation is minimal and so forth, how well can they work when everything is good and to determine whether or not those performances are appropriate for the applications under consideration and whether or not that is good enough.

Okay, and then the third area is in outcomes. If we look at what happens to the deterioration in performance in certain areas and recognize that we need better patient education, better physician education so that we don't have physicians who come to us and say they don't care about accuracy, they look at trending and obviously they don't have a clue about precision, I don't want to hear that again from a physician in front of a panel like this, to be blunt about it. I would also like to see a better reporting of outcomes so that we can determine, as Dr. Rosenbloom has eloquently pointed out, whether we really do, in fact, have a problem that needs to be addressed because resources are scarce and we don't need to spin our wheels solving a problem that doesn't exist.

So I would like to see the goals of our working groups or groups or areas which the FDA works to be in

design to be in performance capabilities and to be in outcomes of both clinical outcomes, performance outcomes in the hands of the public, the consumers, and problems that occur from those groups.

So those are the three things that I have to state about meeting goal number five. There was a gentlemen from the audience who raised his hand. Do you still want to make a brief comment? Please do and then we will move to Dr. Gutman.

DR. DUNCAN: Both Dr. Goldsmith and Dr. Rej expressed an interest in quality control. NCCLS does have a subcommittee that is interested in quality control for these devices at the moment and will have a document out by about July. That is primarily into the laboratory and alternate settings within the hospital or health care settings and not of the consumer but there will be a document out in the near future.

DR. NIPPER: Thank you. Dr. Gutman.

DR. GUTMAN: Yes, well, I first want to thank everyone here and to show you that we from our perspective have gotten our money's worth, certainly out of you and I also think from the folks in the audience, those who are still here and those who may have been worn down and already

left. We really are very grateful that so many people showed such a keen interest and provided us such a panoramic range of perspectives. I think we have a real opportunity here. I know we have a real opportunity here because we probably scared industry into thinking that this would perhaps be different or worse than it was and they are quite committed to working with us, and forming the Nidosphere(?) group and I think we have gotten some advice from this group to make sure that we keep whatever group we form representative of a broader constituency perhaps within FDA and industry. We will try to take that to heart and try to ground it appropriately.

I think we have clearly questioned exactly the nature of the problem but that non-plus doesn't non-plus me at all because I think we can strive to improve where we are at, whether there is a big problem, a small problem or frankly under the TQM concept, you improve where you are at just for the sake of improving where you are at and doing better so 1997 is a good time for us to look at what we can do better, whatever the nature of the problem and we can certainly anticipate that the technology is going to continue to race along in trying to prepare ourselves for it.

We had some notions, some pre-conceived notions maybe you perceived them in the questions that were raised or in reading the Federal Register notice and you have titered them. You have introduced ideas we hadn't even imagined and one of the issues that you as a group and the audience has crystallized a little bit is the dilemma about use and the different ways these are used. I always knew that. I don't know that I appreciated that quite as graphically as I do now.

One of my colleagues in the FDA indicated to me during the break that she knows that in fact there is a problem with use even in the way studies are done and the way studies are supporting other product lines outside of the in vitro diagnostic area in that there needs to be a real appreciation for when a product is supposed to be used, how it is supposed to be used. My response to my colleague, my response to you as well is that we have difficulty dealing with off-label use and with trying to police the general laboratory and research environment. Our general solution to that is through labelling and labelling is an issue we hope to interact with whatever working with groups we have and making more user friendly.

But if, in fact, you have any specific advice on

how we might use labelling, how we might tie into education or how we might use it to bring order into this universe, you might speak now or speak after the meeting or forever hold your peace.

DR. NIPPER: Good. Well, we all welcome Dr. Clement back. I am putting him on the hot seat, letting him tell us about his experiences with patients and labelling and whether or not you think we should be, you should answer that question yes, no, maybe and why.

DR. CLEMENT: I would say yes, obviously the simpler the better in terms of, or simpler but more detailed. Obviously the more user friendly the information is the better. I think possibly including some type of graph as you, Dr. Nipper, portrayed in the actual package insert actually so we can help educate the patient about that when they see a number that there obviously is a 95 percent confidence interval that that would obviously go a long way to help and improve the patient's education and know what that value really means.

I think we can make some improvements on that, I agree.

DR. NIPPER: Yes, Dr. Kimmelman.

DR. KIMMELMAN: I don't mean this to be the last

word and I am sure it is not going to be with Henry up there. I just wanted to make a couple of points. Industry people that you saw out here today are the advocates of FDA within their organizations and the thing that, the worst thing that can happen to those advocates is surprise. Surprise causes loss of credibility on behalf of, by your advocates. It increased costs, it incurs delays. We have a long experience working with the agency with respect to submissions for these types of products and any changes that represent a surprise to us can cause us problems so I would implore the FDA and the panel and anybody else that if there is going to be change in the way these products are regulated either through the submissions process or through labelling or whatever that you keep us informed, keep us part of the process and I think you will find that you have a willing group of industry people to help you. Thank you.

DR. NIPPER: Thank you. Did you want to respond to that, Dr. Gutman?

DR. GUTMAN: No, I am very sensitive to that and will take that to heart.

DR. NIPPER: Dr. Harrington Falls, what do you think about the question on the screen about labelling and yes, no, maybe, why.

DR. HARRINGTON FALLS: I agree that the patients with the devices need more detailed information. I also hope that the people that are working to control their diabetes can get across to them this is what we are going to do and this is why because now that the insulin pump is available, we talked about sliding scale insulins and how people end up chasing their levels and that is really not what we are aiming for. We don't want people to check their sugar and then try to match it because they might not reach a physiologic, a natural physiologic state and we don't know what the long term consequences of that are going to be.

I think if the patients understand this is to help you to optimize your health and then their health care provider works with them, that is going to be where the labelling comes in.

DR. NIPPER: Thank you. Dr. Boughman.

DR. BOUGHMAN: I am reminded of the two old adages. One you can lead a horse to water but you can't make him drink. The other one in preparation for --

DR. NIPPER: That was a male horse she was talking about.

DR. BOUGHMAN: It was not a mare, it was a horse. The other one in learning the process of presenting a

lecture that you first tell them what you are going to tell them and then you tell them and you tell them what you have told them. I am wondering if this isn't a context that in fact we might take a step back and look at the labelling process altogether and put those two old adages that have withstood the test of time in a different way.

If, in fact, the absolutely critical information to perform the test with the device at hand were put in such a way that it could be read and re-read by even those patient who don't read a lot, don't like to read and really don't care what the standard deviations are, some of those patients that only test periodically, for example. If that were separated out and then included in the package insert but in a different place where the more detailed parts of the information, that those patients who wanted to read it, wanted to try to understand it and their health care professionals could read that with them so that the information is there but not, in fact, overlapping with the real critical information, rather than having a bold statement jump out every once in a while to simply look at reorganization of that for ease of use and access to all who wish different levels of access.

DR. NIPPER: Thank you. Ms. Rosenthal, I didn't

mean to skip over you.

MS. ROSENTHAL: I do agree with the statement to provide simple but more detailed description. I would like to see somewhere on the label a warning of some sort, maybe worded perhaps that the DCCT has established that long range complications are related to good control however a diabetic is not expected to have absolutely normal blood sugars at all times because I suspect that many of the adverse circumstances come from hypoglycemia in adolescents or in diabetics who are trying too hard to stay too close to the line and I think that might help a little to have some type of warning in the label.

DR. NIPPER: Thank you. Dr. Habig.

DR. HABIG: The wording of this question gives me a little pause and I can't help but note Habig's laws of paranoia since Dr. Gutman described the industry as possibly being paranoid. Law number one is it pays to be paranoid and law number two is just because you are paranoid doesn't mean the bastards are not out to get you.

So here is my problem with that is that the FDA doesn't provide labelling, manufacturers do. So the wording is just a little bit difficult. FDA might prescribe in a guidance document what the contents of labelling should be.

DR. GUTMAN: That was the intent.

DR. HABIG: I am just being very careful. I think guidance in that manner would be useful.

DR. NIPPER: We want to know if that question is safe and effective as well.

DR. HABIG: Oh, you mean I get to judge? It is effective but it is not safe. I think such labelling ought to come from the user primarily. The patients, the diabetic educators ought to be able to help us from what kind of labelling would serve them best and then the FDA and industry could figure out how best to present that.

DR. NIPPER: Thank you. Dr. Rej?

DR. REJ: There is that words more. More detailed than what?

DR. GUTMAN: Than what we only see now. Sometimes what we see now is pretty damn good and sometimes it may be not so good so maybe we can establish some kind of a minimal labelling threshold or encourage, perhaps not require.

DR. REJ: More detailed than the 19 points that are on the current document?

DR. GUTMAN: Well, maybe it needs to be more simple than the 19 points. Maybe we only need three. I don't know.

DR. REJ: It seems that most aspects are covered. Maybe not as simply as they could but I think as a guidance document of manufacturers, this seems like a good start point. I didn't see too much that was really missing. I think it is the way Dr. Boughman put it, it is presented to the readers of this label rather than the FDA direction.

DR. GUTMAN: Part of this is also the distinction between the different levels of use, between professional use and home use and perhaps research use and various odd uses and some of the manufacturers actually have some pretty innovative ideas on ways. Actually it parallels the way you have which is maybe you have more than one package insert to do more than one thing.

DR. REJ: I would definitely encourage that there be adequate labelling for each of the intended uses, definitely.

DR. GUTMAN: And with an effort to make it as simple as possible for the home user and then for the professional user to let them know what they are or are not buying.

DR. REJ: Again, I was interpreting the question in the context of the home use use of the home use devices.

DR. GUTMAN: And what we would do, frankly, what

we often do in the history of our review process, the manufacturers are our best instructors because the ones who really do good reviews and who write good labels, then for the ones who don't research good reviews and don't write such good labels, they are penalized because some of their competitors do good work and what we would hope is that the best of the manufacturers would contribute some kind of insight, some templates, that we could use and hopefully share the wealth, share the minimum or share the good ideas so that there is a more universal filtering of user friendly, simple language.

MR. COOPER: Of course, the FDA knows that we are being totally overly simplistic in discussing this because in our industry representative who was concerned about speed, rapid changes or surprises, if we do it right there won't be any surprises because it seems to me the first task is to determine what the critical elements of information the consumer needs to have and we have not done that so that will clearly take time.

Then after it is determined what are the critical elements of information that the consumer needs to have, we have to determine what is the best way to get that information to the consumer. Our own research, for example,

indicates that consumers not only do not understand simple graphs such as the Nipper graph but won't even look at them so all of that process has to, while it may turn out to be important information, it may turn out to be the very wrong way to give it to them.

So I would, obviously we are simplifying and obviously it would take a long, long time.

DR. NIPPER: Dr. Zawadzki.

DR. ZAWADZKI: I would agree with Dr. Habig that there are already models available from industry sources that provide a lot of this information. I think the uniformity and the question that Dr. Cooper raised regarding what issues need to be included does need to be revisited.

DR. KURT: I would suggest the labelling that would be more user friendly such as user friendly language for dummies as the dummies series or the stupid series goes. I was shocked yesterday afternoon that there is certain words such as reagent and in vitro required and I am not certain how many people outside of the medical field are really going to understand what reagent and in vitro mean and I would suggest that you allow those to be included in the parentheses with more simply understood language as phrases before them or included in a vocabulary description

at the end or something rather than requirement of the use of such technical words.

DR. NIPPER: Thank you. Dr. Rosenbloom.

DR. ROSENBLOOM: On the surface, simple but more detailed sounds like an oxymoron, but I think there are ways of, which are familiar to everyone here of making the language, providing a lot of information but making the language understandable and not using big medical words. The question is getting people to read those things. It would be interesting to know how many people who use meters that they have been taught, a meter system, that they have been taught in the clinic how to use which they have to be or they should be, how many have gone back and read through the text of the labelling and I suspect that very few have. Most people rely on the instruction that they receive and if something goes wrong, they will call the company and how many calls to the company, for example, could have been solved if someone had just read the instruction manual.

I suspect that 80 percent or so so I am not sure that labelling is the answer to improving patient quality control. It might be that video instruction or maybe newsletters, more digestible forms of information. I think one needs to look at the entire issue and look for the most

efficacious approach to educating patients and health professionals, particularly non-diabetologists, health professionals. I don't think labelling is the answer.

DR. NIPPER: Thank you. Dr. Goldsmith.

DR. GOLDSMITH: I agree that a simple approach, making wording as simple as possible to the lay person is very important and I agree with your comment of the video if it is possible. I know there is a cross-detection that not everybody has access to VCRs but certainly pictures tell the whole story. Just as an example, NCCRS has put out a newborn screening video tape that a variety of health care workers collect those samples from neonates. That technique is not always so good and that has come a long way in helping make that more standardized and uniform so I think that is a good medium.

DR. NIPPER: Thank you. Dr. Rej, you had a comment.

DR. REJ: It relates to graphic that came before this one. We didn't get a chance to get to it and I have some views on each of the points. By use of a specific reference methodology within the manufacturer's shop comparing a or in some study, correct, is that looking at the individual glucose meters or results from a type of

device with a single reference method?

DR. GUTMAN: Yes, that is an extremely challenging question, the way it was cast was and I thought it was too parochial for this point in time and asked Dr. Nipper for further discussion in the working group. The point was, is there some interest in trying to establish if not a uniform reference methodology against which to cast all the devices away to trace them uniformly.

DR. REJ: I think we heard a few presentations today and yesterday that some of the confusion that exists exists because there has been a sliding scale that has been one meter used here, a reference meter used here, another reference system used here and I think that the need for using a specific methodology may not be necessary in an individual study; however, that method should somehow be tied in. There should be some traceability of that method to I think the national reference system credentialed method of the CDC hexokinase procedure. It seems to be the method of choice and while I don't think that it is necessary for all devices to be referenced or compared to that method, the method that it is being compared to should be so that at least it is a second, the traceability of the reference method used is traceable to that standard which is then

credentialed as the U.S. standard for that.

I think statisticians can probably answer question number two but my sense is that there should be, assuming by minimum you mean minimum number, and I don't feel qualified to answer that but my gut recommendation would be yes, I think it should be a minimum number. I am involved in setting standards in New York and I know whenever you say there should be sufficient, you say, well, give me a number and I say 39 and they say why 39.

So it is always a two-edged sword but I think you have the statistical manpower and womenpower to pick it up but my sense is that you should have at least a bottom end number.

In terms of the actual goal, by that question do you mean do you want a number for each or one of those approaches?

DR. GUTMAN: Any of them.

DR. REJ: I think you should go with the total error approach. I think that is what is being generated by the system and you can have some numbers or some suggested numbers for individual components but I am a firm believer in terms of total error in terms of minimum performance standards.

DR. NIPPER: Thank you. Are there any other comments? We are getting down to the knot in the end of the road. Are there any other comments from the panel before I turn the meeting over to Sharon for some nitty gritty information? Hearing none, are there any brief statements from people from the audience who have heard what we just said? Hearing none, Sharon?

MS. LAPPALAINEN: I would just like to remind those of you that are left that the docket will remain open until April 3 for comments from the public concerning the five goals or any of the seven topics. You can make those, you can send those to me, Sharon K. Lappalainen at the Center for Devices and Radiological Health. The mail stop is HFZ-440, Food and Drug Administration, and the address is 2098 Gaither Road, Rockville, Maryland, 20850.

The last thing, the next meeting for the Clinical Chemistry and Toxicology Panel is tentatively scheduled for July 24 and 25, 1997 and that is a tentative date. I hand it to you, Dr. Nipper.

DR. NIPPER: Thank you. I was reminded by Dr. Goldsmith that that is probably the AACC meeting. NO, it is not --

DR. GOLDSMITH: The following week. I just

checked.

MS. LAPPALAINEN: I checked.

DR. NIPPER: I would like to close the meeting with my personal thanks to everyone from the FDA who made my initial meeting as chair of the panel as very good one as far as my personal feelings go. I liked the idea that we were working on a problem and working towards solving problems rather than picking holes in things and trying to figure out whether we could let something in or out. It was a constructive experience for me and I hope for all of you.

I would also like to thank the manufacturers' participants who came. They were very helpful in their presentations and went, I hope that this will give us the catalyst to move forward to making better patient care for those people with diabetes. I think that we are all in the caring industry for whatever purposes and I think we all do better when people do better healthwise.

With those remarks, I would like to adjourn the meeting. Thank you.

(Whereupon, the meeting was adjourned at 4:30 p.m.)